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DIFFUSE LUNG DISEASE: CLINICAL AND RADIOLOGICAL FEATURES.[1]

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THE title diffuse lung disease, strictly interpreted, would imply a review of most affections of the lungs and many of those of the heart. Such a performance would be both dull and fruitless, and it is proposed to restrict the subject matter of this symposium quite arbitrarily. We shall consider briefly those conditions only in which new abnormal material is present throughout the lungs—such things as fibrous tissue, neoplastic tissue, dust and various infiltrates. Emphysema and vascular lesions of the lungs we shall overlook, diffuse lung lesions though they may be.

Figure I is a useful diagrammatic classification of diffuse lung lesions of the sort under discussion. It is an anatomical classification with certain physiological implications. In the centre is represented the normal lung structure—elastic, easily distensible and so constructed as to allow maximal contact between the inspired air and the pulmonary capillary blood.

In the first abnormal group (Figure I, upper right) there is diffuse thickening of most or all alveolar walls throughout the lung. Such a pathological process will interfere with two aspects of normal lung function: it will make the lungs less distensible than normal, and it will interfere with oxygen transfer across the alveolar-capillary membrane. The classical example of this group is the diffuse interstitial pulmonary fibrosis of Hamman and Rich. The same process is seen in one of the pneumoconioses, asbestosis, as well as in that peculiar tumour, adenomatosis or alveolar-cell carcinoma.

In the second group (Figure I, upper left) there are nodules of abnormal tissue within alveolar walls in many parts of the lung. At the microscopic level it is a much more spotty process. Odd, scattered lesions represented in the top part of the section may interfere little if at all with lung function. When the lesions become as widespread as in the lower part of the section, the situation is, functionally speaking, very close to that of our first group. The granulomata dominate this group, with miliary tuberculosis and sarcoidosis the most common clinical examples. A second pneumoconiosis, berylliosis, may produce the same anatomical and functional picture.

[1] Presented at a plenary session of The Royal Australasian College of Physicians with the Australian Thoracic Society (formerly Laennec Society of Australia) in Sydney on October 12, 1960.

In the third group (Figure I, lower right) the abnormal tissue is distributed predominantly along the lymphoid and lymphatic pathways—that is, mainly in the interlobular septa and around the tiny bronchovascular bundles. It may interfere considerably with lung distensibility, but hardly at all with alveolar gas exchange. As might be expected, the commonest clinical examples in this group are those due to malignant disease—lymphatic permeation by secondary malignancy or proliferation and infiltration by the lymphomata.

The last group (Figure I, lower left) consists of lesions with no respect for the intricacies of pulmonary anatomy. They are just lumps that lie in the lung. Until they become very extensive and replace a great deal of respiratory tissue, they may be associated with little functional disturbance. In this group disseminated malignant disease again ranks highly, with a third pneumoconiosis, silicosis, another good example.

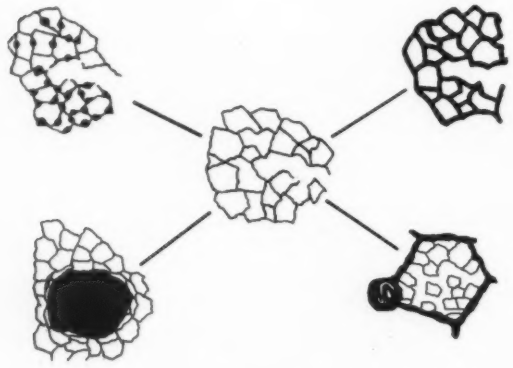

FIGURE I.
Diagrammatic classification of various forms of diffuse lung disease. See text for description.

The clinical features associated with these conditions are fairly well known. To a major extent they will depend on which of the above groups we are dealing with. Many patients are relatively asymptomatic even in the presence of extensive radiological shadows in the chest X-ray film, while in others symptoms may precede radiological abnormalities by many months.

Dyspnœa is the commonest major symptom. It is commonest in those patients with diffuse thickening of alveolar walls, those with interlobular infiltration and those with a very extensive nodular lesion of the alveolar walls. It is due to the increased rigidity of the lungs and the increased muscular work involved in expanding them. In some conditions the dyspnœa may be rapidly and relentlessly progressive—in lymphangitis carcinomatosa and in the acute variety of the Hamman-Rich syndrome. In others, the onset of dyspnœa is insidious and progression barely perceptible.

The second major symptom is cough. With a few notable exceptions it is dry and unproductive. In the gravely disabled patient episodes of severe cough may lead to an alarming degree of cyanosis and general distress. This persistent, dry cough seems to be most common in malignant infiltration of the lung and in diffuse pulmonary fibrosis—in both it may antedate the onset of significant dyspnœa. By contrast, patients with pulmonary adenomatosis may cough up enormous quantities of mucoid sputum.

Hæmoptysis is relatively uncommon among the conditions we are considering. Sometimes patients with diffuse pulmonary fibrosis may cough up a little blood, but collagen diseases involving the lung and vascular secondary deposits from chorionepithelioma and thyroid carcinoma provide most of the significant hæmoptyses encountered.

Physical examination in the average case is relatively unrewarding, but since the yield of diagnostic clues is at least as high as in any other non-operative method of investigation it should not be skimped.

Clubbing of the fingers is commonest in the group in which the alveolar walls are diffusely thickened. One sees it frequently in cases of the Hamman-Rich syndrome and of pulmonary asbestosis, in both of which conditions it may reach drum-stick proportions. Some regard it as a *sine qua non* for the diagnosis of the Hamman-Rich syndrome, although this is far from being the case. Finger clubbing is distinctly rare in all groups other than those with diffuse thickening of alveolar walls. The mechanism of its production is completely obscure in diffuse lung disease. It is palpably not a mere reflection of arterial hypoxia, and no really worthwhile evidence has been adduced as to its pathogenesis.

Clinical cyanosis is another sign frequently recorded. In a minority of patients this clinical impression is confirmed by the results of blood gas studies. In fact, once a spectacular X-ray film of the chest has been produced, cyanosis is grossly over-reported (by the writer among others) in patients with diffuse lung lesions. Central cyanosis is seen with any frequency only in the group with diffuse thickening of alveolar walls; even then it is relatively uncommon at rest, but may appear or increase on exercise.

Examination of the chest itself seldom provides diagnostic information. There may be no clinical signs at all. Melville Arnott has referred to the "door-stop" sign: as the patient takes a deep breath to lift the examiner's hands, inspiration ceases abruptly after a small excursion rather than tapering off—palpable evidence that the patient who says he cannot take a deep breath is perfectly correct. Auscultation sometimes reveals showers of fine crepitations over the whole of both lung fields. These may be here today and gone tomorrow, or they may be extraordinarily persistent. Beyond implying a finely disseminate lesion they provide no diagnostic help.

Further examination may reveal evidence of pulmonary hypertension or frank congestive cardiac failure—both most common once more in the patient with diffuse thickening of alveolar walls. In patients with considerable dyspnœa, weight loss and wasting are not uncommon—reflections of the high energy cost of constantly breathing under difficulties.

The isolated abnormality in any part of the body must be avidly sought, for it may provide the clue that will save the patient a lung biopsy. Peripheral evidence of rheumatoid arthritis, scleroderma or a frank collagenosis may provide strong inferential evidence as to the nature of a diffuse lung lesion. The finding of a tumour of breast, gonad or gastro-intestinal tract may direct diagnosis more constructively than an approach via the lungs themselves. Enlarged lymph nodes, cervical or peripheral, may provide more accessible biopsy material than the lung parenchyma.

Especially in the absence of extrapulmonary findings, the history should be explored and reexplored for diagnostic evidence. An industrial history is seldom omitted, but it is important to obtain as specific a history of dust exposure as possible. Three pneumoconioses (beryllosis, asbestosis and silicosis) were used as illustrations to the classification theme, not least because they produce three quite different pathological pictures. A fourth contrast is provided by coal-workers' pneumoconiosis which does not fit into the classification at all. The diffuse nodules of simple coal-workers' pneumoconiosis shown on an X-ray film correlate well with the total amount of coal dust in the lungs—indeed they should do so, because coal dust causes the shadows; but the symptoms and the disability are due to focal emphysema, the extent of which may bear no close correlation with the radiologically determined category of pneumoconiosis at all.

The radiological features of the group of conditions under discussion have been the subject of numerous lengthy descriptions. In general terms we expect to see diffuse or scattered shadows of some sort in the chest X-ray film. This is usually but not invariably so. The chest X-ray film may be completely normal in the presence of widespread pathological changes and severe clinical disability. I have recently had under my care a patient who has gross diffuse pulmonary fibrosis (proven by biopsy) in the presence of a normal chest X-ray film, and a similar situation sometimes arises in pulmonary asbestosis (Williams and Hugh-Jones, 1960). It is not rare for patients with secondary malignant disease (especially of the breast and the stomach) to complain of a hacking, dry cough and some shortness of breath for some time before one can be sure of the presence of lymphangitis carcinomatosa on the chest radiograph. *Per contra*, we have already mentioned that patients with few or no symptoms may have spectacularly abnormal chest X-ray films.

In assessing the abnormal chest radiograph there are a number of features to be closely examined (Figure II).

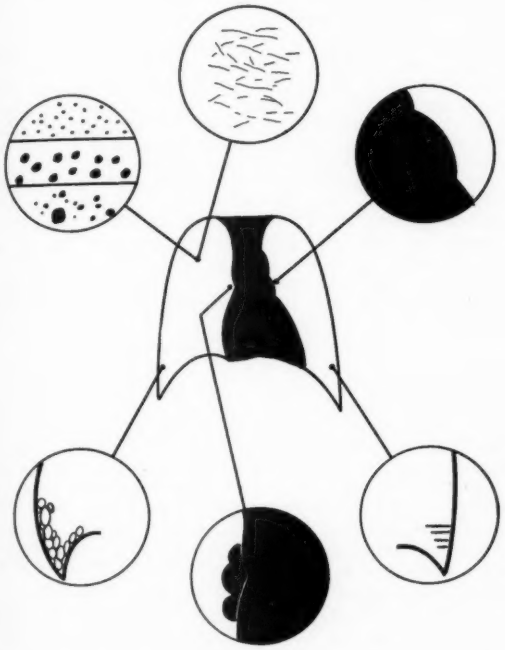

FIGURE II.

Some features to be examined in the chest radiograph in diffuse lung disease. *Upper left* and *upper centre*: the nature of the lesions. *Lower centre*: the presence of enlarged mediastinal lymph nodes. *Lower right*: Kerley's B lines. *Upper right*: enlargement of pulmonary artery. *Lower left*: presence of cysts.

None of these features are diagnostic—they provide clues only. We try first to assess the disseminated shadows themselves—are they dots or lines? If dots, are they small or large? Are they all about the same size? The inferences which may be made about the nature of the lesions are obvious. Diffuse infiltrations of alveolar walls or interlobular septa are likely to produce linear shadows. (It is hard to conceive of thickened alveolar walls ever producing radiological shadows; it is highly likely that in diseases such as the Hamman-Rich syndrome the linear shadows are due to accompanying fibrosis of interlobular septa.) The granulomata tend to produce a nodular or micro-nodular appearance, and metastatic deposits a more lumpy appearance. At times, any distinction between linear and nodular shadows may be extremely difficult, even with a first-class radiograph.

One looks next for other appearances associated with the diffuse radiological lesions. There may be cysts present. These may be so extensive throughout both lung fields as to produce the picture of so-called "honey-comb lung"—an appearance seen in many different pathological conditions. In asbestosis, single or multiple isolated cysts may be seen in any part of the lung fields. Cysts may sometimes be concentrated in the lower and posterior portions of the lungs, prominent in the costo-phrenic angles in both postero-anterior and lateral chest radiographs. This latter appearance has been regarded by some as characteristic of the lung in scleroderma. But it may occur in any of the chronic pulmonary fibroses.

The presence of Kerley's B lines above the diaphragm in the absence of heart disease strongly suggests lymphatic permeation and should make one think at once of malignant infiltration of the lung. The shadows of enlarged hilar and/or superior mediastinal lymph nodes directs thinking towards sarcoidosis or one of the lymphomata. A shaggy border to the mediastinal shadow has been regarded as common in asbestosis, but Williams and Hugh-Jones (1960) found that observers differed considerably in their interpretation of this appearance.

Finally, before leaving the chest radiograph, one looks for radiological evidence of pulmonary hypertension.

What then should be one's clinical approach to the patient with a diffuse lung lesion? The importance of a careful history, a complete physical examination and a detailed scrutiny of the chest X-ray film has been emphasized. In some cases formal tests of respiratory function will indicate the presence of a diffuse lung lesion when the radiological appearances are normal or equivocal; in the remainder they will provide an accurate and objective assessment of the nature and degree of the incapacity. Other laboratory investigations are only occasionally helpful in diagnosis. (However, they may be crucial, as in, say, the demonstration of tubercle bacilli in the sputum of a patient with miliary tuberculosis.)

In most cases, then, we are left with no clear ætiological or pathological diagnosis at this stage; and one must decide just how far one ought to go in achieving a tissue diagnosis in each individual patient. The two biopsy procedures which may be of value in this regard are, of course, lymph node biopsy and lung biopsy.

Palpably enlarged peripheral lymph nodes may yield convenient biopsy material and a firm diagnosis. In the absence of enlarged peripheral lymph nodes, scalene node biopsy plays an important role in diagnosis in some diffuse lung lesions. The yield is highest when the chest X-ray film shows enlarged mediastinal lymph nodes, but it is a reasonable preliminary procedure to recommend in any patient in whom lung biopsy is being seriously considered. Only in sarcoidosis, the reticuloses and in malignant disease can positive results be expected; and a negative result has no exclusive value even when one of these conditions is suspected.

Lung biopsy, widely acclaimed as safe and certain, requires more careful consideration. It will certainly provide a pathological diagnosis, though often not an ætiological one. It requires a thoracotomy, it is not free from morbidity, and whilst I have not seen it lead to death, I have seen some parlous "near-misses". It seems to be variously over-used and under-used. Certainly those who never recommend it are passing up a valuable diagnostic method; those who regard it almost as part of the routine investigation of a patient with a diffuse lung lesion are submitting some of their patients to an unwarranted hazard. The decision is often difficult, and perhaps the major guiding principle should lie in the answers to two questions: (i) May this patient have a lesion which is amenable to treatment? (ii) Would I regard treatment as indicated or necessary if I found exactly what I expected?

In my own hands, asking these two questions has reduced rather than increased the number of lung biopsies

I have requested. Looked at objectively, the number of diffuse lung lesions which can be efficiently treated on the one hand or need be treated on the other is not great. One is more likely to recommend lung biopsy the younger the patient and the more progressive the symptoms. It is hard, for example, to justify lung biopsy in a middle-aged to elderly patient with few or no symptoms, who happens to have a diffuse radiological lesion in his chest, when the main result will be to affix a label to his disease.

What are the treatable diffuse lung lesions? They are, as we have mentioned, few: miliary tuberculosis, sarcoidosis, some of the collagen diseases, some examples of the Hamman-Rich syndrome and, very rarely, secondary malignant disease of the breast. The available therapy will be one or other of prolonged chemotherapy, prolonged steroid therapy or bilateral adrenalectomy — no light decision in any individual case. Even then, we may immediately confound matters by pointing out that some patients with diffuse pulmonary sarcoidosis recover without steroids; that many patients with the Hamman-Rich syndrome or a collagen disease fail to gain benefit from steroid therapy; and that diffuse pulmonary infiltration by breast carcinoma is regarded by some as a contraindication to ablative endocrine surgery.

If the therapeutic yield is poor, we and our patients may derive some consolation from the fact that many diffuse lung lesions run a relatively benign course. The diffuse fibroses, no matter what their origin, are frequently much more spectacular radiologically than symptomatically. Even in the Hamman-Rich syndrome, chronic, almost static, examples are much commoner than acutely progressive ones, and merit no active treatment. The dust diseases vary enormously one to the other in their degree of clinical disability. Even in the case of malignant disease the outcome is not necessarily rapid. Examples are not rare of so-called benign metastasizing goitre—the chest X-ray film being crowded with the shadows of nodules of thyroid carcinoma—with survival for three to five years; and a similar situation may occur with multiple secondary deposits from a hypernephroma.

To underline my theme that therapy has unfortunately not kept pace with diagnosis in diffuse lung disease, I tried to compare my clinical performance in the last 12 months with what Laennec might have achieved 150 years ago. Sixteen patients with diffuse lung lesions attended my clinic in the year. Scalene node biopsy gave no positive diagnoses (this is fortuitous, and reflects the particular patients involved). Five patients were submitted to lung biopsy, and after this procedure three were actively treated—all with steroids. One patient's condition improved a great deal, one patient remained unchanged, and in one case steroids may well have done more harm than good. I concluded that my diagnoses were probably much more accurate than Laennec's, but therapeutically the advance seemed disappointing.

Summary.

Diffuse lung lesions may be classified on the basis of the distribution of the pathological lesions in the lung. Such a classification has important implications in terms of the resulting clinical picture. Precise diagnosis is difficult on clinical and radiological grounds, and often leads to no specific therapy. In each individual patient the potential risks and benefits should be carefully balanced in planning the more hazardous diagnostic procedures.

Acknowledgements.

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CHRONIC DIFFUSE INTERSTITIAL PNEUMONIA AND DIFFUSE INTERSTITIAL PULMONARY FIBROSIS.[1]

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THERE is a group of diseases each of which begins as an inflammation of the alveolar wall, the peribronchial and perivascular connective tissue and the interlobular septa, which are collectively called the interstitial tissue of the lung. If the condition runs its full course the end result will be extensive fibrosis in these areas.

Normal Alveolar Wall.

The changes in the alveolar wall are the most important ones and it is therefore relevant to recall the normal structure. The wall is made up of two layers of alveolar epithelium enclosing capillaries which are supported by reticulin and elastic fibres, connective tissue ground substance and an occasional strand of collagen. All these can be seen microscopically in sections stained in the appropriate manner. The capillaries form an anastomosing network which weaves amongst the fibres. Fibrous tissue cells are rarely seen in healthy alveolar walls (Figure I).[2]

When viewed with an electron microscope the alveolar epithelial cells have a widely-spread, thin layer of cytoplasm completely lining the alveoli. Gases passing from the inhaled air to the blood traverse the cytoplasm of the epithelial cell, then a "basement membrane" which includes connective tissue ground substance and fibres and finally the attenuated cytoplasm of an endothelial cell. The total distance is about 0·5μ. Any significant increase of this distance, as by thickening of the basement membrane, will impair the diffusion of gases.

Figures II and III, which illustrate these points, are from photographs taken by Associate Professor D. A. Cameron of this department. The tissue was fixed in osmium tetroxide and examined with a Philips electron microscope.

First Stage of the Disease.

From a study of many lungs and from descriptions in the literature, it is apparent that there is a pattern of disease which advances by four well-defined stages. The evidence for this comes from animal experiments on irradiation (Warren and Gates, 1940), from the progressive changes seen in human lungs between the time of a biopsy and a post-mortem examination, and from the observation of more than one stage in lungs at one time.

In the first stage the changes occur in fairly large areas of the lung and these are darker and heavier than usual, but not airless and consolidated.

Under the light microscope (Figure IV) the main change is seen to be a thickening of the alveolar walls which is due to dilatation of the capillaries, swelling of their endothelial cells and some œdema. There is an infiltration of macrophages, a few of which are very large and of unusual appearance, and there are some lymphocytes and plasma cells. More macrophages lie free in the alveoli or on the alveolar epithelium. Also within some alveoli there is a fibrinous exudate pressed against the walls to form a hyaline membrane. Focal hæmorrhages may be present.

Similar but less conspicuous changes occur in the septa and around the bronchovascular bundles.

Second Stage.

From the first stage the lung may return to normal or it may pass rather slowly into the second stage (Figure V), in which the main feature is a proliferation of reticulin fibres in the alveolar walls. These are still

[1] Delivered as part of a symposium at a plenary session of the Australian Thoracic Society and The Royal Australasian College of Physicians held in Sydney on October 12, 1960.

[2] For Figures I to VII and Figure IX see art-paper supplement.

thickened by dilated capillaries. Macrophages are usually less numerous and special stains may show that elastic fibres are degenerating.

Third Stage.

The third stage (Figure VI) is reached when fibroblasts and collagen appear in excess in the alveolar walls. Generally it is thought that the collagen is laid down within the alveolar wall, but the examination of sections suggests that organization of the hyaline membranes also plays a part (Hadfield, 1938; Ogilvie and Hulse, 1954). There are many other changes, including a reduction in the number and size of capillaries, the appearance of cuboidal or rather lower epithelium and even the destruction of some alveolar walls. In the alveoli there will be some macrophages; in other areas exudate or hæmorrhage will have been organized.

About the bronchi and large vessels and in the interlobular septa fibrosis has occurred and consequently expansion of the lung is restricted. Hæmosiderin has been deposited in small patches of lymphoid tissue as a result of the focal hæmorrhages. The walls of the arterioles are thickened, reflecting the pulmonary hypertension brought on by the restricted capillary blood flow and the lowered level of oxygen in the blood.

At this stage the affected lung tissue is tough, rubbery, and easily cut into thin slices.

In order to present a consecutive story I have simplified it a little. Not all the affected parts of the lung are at the same stage at one time. Variations of the pattern are seen and I shall mention these later. Nevertheless, there is a sequence constituting a disease process which could reasonably be called chronic diffuse interstitial pneumonia. The term diffuse interstitial fibrosis is not suitable for the purpose as it describes one stage only.

The patient may die in this third stage, or even in the second, from anoxia due to impaired diffusion and increased rigidity of the lung or from failure of the right side of the heart.

Fourth Stage.

If the patient survives, changes occur in one of two main directions. The fibrous tissue may, by contracting, render the affected parts dense and airless (Figure VII). This is the compact pulmonary sclerosis of Getzowa (1945).

On the other hand, the lung may become cystic (Figure VIII), forming one type of honeycomb lung. There is no agreement as to what parts of the air passages form the cysts, and opinions as to their origin range from dilatation of bronchioles down to the rupture of many alveolar walls.

The cysts, which are generally not more than 1 cm. in diameter, have a fibrous wall and an epithelial lining which is often ciliated (Figure IX).

Eventually the patient dies of anoxia, heart failure or, in honeycomb lung, from spontaneous pneumothorax or carcinomatous change in the lining epithelium (Collins *et alii*, 1958).

Variations.

This central pattern of disease is seen with a number of variations.

The speed of the process may vary so that the time from onset to death with fibrosis may be a few months or many years. When the rate is slow the first stage will be modified or perhaps absent.

The volume of lung affected varies. If small areas only are diseased, then there may be no signs or symptoms. I have found such patches of interstitial fibrosis in patients who have died of quite unrelated disease.

The number and type of inflammatory cells vary a great deal. For instance, in some affected lungs there are many lymphocytes. The degree of uniformity of the fibrosis also varies and there is no sharp line between the disease pattern described and the more nodular lesions typical of sarcoidosis and other conditions.

In a few patients there will be necrosis of some pulmonary arterioles.

Ætiology.

First let me make it quite clear that I am not considering all patients with alveolar wall fibrosis, but only those who have arrived at that state by the steps I have described. Amongst other conditions this excludes chronic passive congestion (Andrews, 1957), pulmonary adenomatosis and congenital alveolar dysplasia of lungs

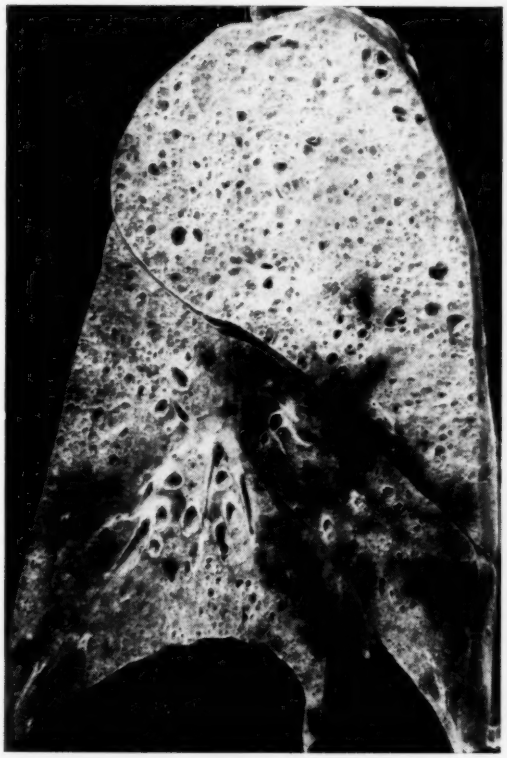

FIGURE VIII.

Lung; this is from a girl, aged 17 years, who died after a year of breathlessness. No cause for the lesion was found. The cystic changes constitute one type of honeycomb lung and illustrate an appearance that may be seen in the fourth stage of the disease.

(MacMahon, 1948). There are many causes of this disease pattern, and in the time available I can give only a few examples under each heading.

Collagen Diseases.

Scleroderma is a well-known example. Progress is usually but not always slow, and fibrinoid necrosis of vessels can sometimes be seen in the lung as elsewhere in the body (Mahrer *et alii*, 1954; Read *et alii*, 1960). Slow changes are also seen in rheumatoid arthritis (Christie, 1954; Cruickshank, 1959).

The lung changes sometimes seen in rheumatic fever are also of this pattern (Gouley, 1938; Hadfield, 1938). When the changes go on to fibrosis the speed of the process is much faster than in scleroderma. Specific Aschoff bodies may be present.

Infection.

The lung changes I have described are seen in scrub typhus and other rickettsial diseases (Allen and Spitz, 1945), in histoplasmosis (Anderson, 1949) and in toxoplasmosis (Pinkerton and Henderson, 1941). The organisms

concerned are all ones which must live within a cell. The disease is acute in scrub typhus and usually stops short of fibrosis. The causative organisms can be found in large mononuclear cells in rickettsial diseases and in toxoplasmosis.

Chemicals.

Several drugs are thought to be a cause, on varying amounts of evidence. Hexamethonium is one (Morrow *et alii*, 1953; Peterson *et alii*, 1959), and mepacrine (Hayden, 1960) is another. The changes have followed the development of hypersensitivity to the drug or the use of an excessive dose.

Irradiation.

The changes are fairly slow and follow the common pattern (Thomas and Forbus, 1959; Warren and Gates, 1940). Round-cell infiltration is said to be frequent.

The Presence of Several Other Diseases.

A number of other diseases are known to be associated with these lung changes. They include nephritis and uræmia (Doniach, 1947; Parkin *et alii*, 1955), Hand-Schuller-Christian disease and related conditions (Bodian, 1955; Oswald and Parkinson, 1949). It is difficult to see any common factor among all the diseases in which this lung pattern is found, but an increased capillary permeability has been suggested (Doniach, 1947).

In the Absence of Other Disease.

The lung changes described may occur in the absence of other recognizable disease. Some attempts have been made to subdivide these cases into groups.

Hamman and Rich (1944) described an acute disease which they saw in four patients, all of whom died within six months of the onset. To this they gave the name of acute diffuse interstitial fibrosis of the lungs. No cause was found but changes in the lungs fit in to the pattern I have described.

Many subsequent authors have enlarged the concept of the Hamman-Rich syndrome to include almost all cases of diffuse interstitial fibrosis of unknown ætiology (Annotation, 1958; Baglio *et alii*, 1960). Scadding (1960) supports this view, but prefers to call the disease chronic diffuse interstitial fibrosis of the lungs, which is, he states, "a syndrome recognisable with confidence on clinical, radiological and physiological features". The disease runs a longer course than that described by Hamman and Rich (1944).

John Read (1958 *a* and *b*) has brought forward evidence that some of the cases of uncertain ætiology are suffering from an auto-immune reaction. His evidence includes (i) the presence of eosinophil leucocytes; (ii) the similarity of the changes in the lung to those in some collagen diseases commonly regarded as being due to hypersensitivity; (iii) the efficacy of cortisone in controlling the progress of the disease in some patients; (iv) Read's experiments with anti-lung serum which evoked similar changes in rats. I have been able to add a little to these experiments, mainly by showing that serum prepared in the way Read used does contain specific anti-lung antibodies as shown by an agar-diffusion technique.

On the evidence available from examination of the lungs, a pathologist can recognize no clear subgroups of these patients, except perhaps, that described by Read. Further investigation will discover other causes. Meanwhile we have no firm evidence on the ætiology of these cases. When the terms Hamman-Rich syndrome or chronic diffuse interstitial fibrosis are used we are admitting our failure to recognize the cause of the pulmonary change.

My conclusion is then that there are many causes of chronic interstitial pneumonia leading to diffuse interstitial pulmonary fibrosis, and that thorough investigation is indicated before relegating a patient to the group known as Hamman-Rich fibrosis or to any other group of unknown ætiology.

Acknowledgements.

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Legends to Illustrations.

FIGURE I.—Normal lung (× 50).

FIGURE II.—Normal lung viewed by the electron microscope (× 13,000). The nucleus is of an endothelial cell lining a capillary (Cap. Lumen) in an alveolar wall. The attenuated cytoplasm is separated from that of an alveolar epithelial cell (Ep. Cyt.) by a basement membrane (B.M.).

FIGURE III.—Normal lung viewed by the electron microscope (× 13,000). The nucleus belongs to an alveolar epithelial cell whose cytoplasm (Ep. Cyt.) with inclusions can be traced to each side. The basement membrane is marked B.M.

FIGURE IV.—Lung (× 50), illustrating the changes in the first stage of chronic diffuse interstitial pneumonia. The alveolar walls are thickened and there is some exudate in the alveoli. Inflammatory cells have infiltrated into the walls and exudate. The changes were caused by irradiation.

FIGURE V.—Lung (× 50); the second stage of the disease is illustrated by this tissue from a patient with scleroderma. The alveolar walls and interlobular septa are thickened. Reticulin fibres were shown, by special stain, to have proliferated.

FIGURE VI.—Lung (× 50); the third stage of the disease is shown by this lung which is from a boy, aged 15 years, who had had rheumatic fever one year before his death. There is now dense fibrosis of the alveolar walls. Arterioles are thickened.

FIGURE VII.—Lung (× 50); this section, which shows the compact pulmonary sclerosis frequently seen in the fourth stage of chronic diffuse interstitial pneumonia, is from the lung of a woman, aged 26 years, who had suffered from rheumatic fever. The fibrosis is more dense than in the second stage and there is less air. In the upper right hand corner is a thickened arteriole.

FIGURE IX.—Lung (× 50); a section from the lung illustrated in Figure VIII shows that the cysts have a fibrous wall and an epithelial lining.

DIFFUSE LUNG DISEASE: PHYSIOLOGICAL FEATURES.[1]

By JOHN READ, M.D., M.R.A.C.P.,
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IN this consideration of some of the physiological disturbances encountered in patients with diffuse lung disease, we shall restrict ourselves to a discussion of the group of conditions discussed in the first section of this symposium (Read, 1961*b*). In classifying these conditions it was pointed out that there may be two major disturbances of normal respiratory function: the lungs may be stiffer than normal, and there may be interference with gas transfer across the alveolar-capillary membrane. These disturbances are represented diagrammatically in Figure I.

The first disturbance is reflected by an alteration in the compliance of the lungs. If a normal subject in making an inspiratory movement produces a transpulmonary pressure gradient of 1 cm. of water, his lungs will expand by about 120 ml., and the compliance of his lungs is expressed as 0·12 litre per centimetre of water. If a patient has diffuse thickening of the alveolar walls throughout his lungs they will become more rigid than normal and provide a greater resistance to expansion. A transpulmonary pressure gradient of 1 cm. of water may only produce 60 ml. of lung expansion; the compliance of his lungs will be expressed as 0·06 litre per centimetre of water—that is, half that of our normal subject. If another patient has considerable replacement of lung tissue by nodules of abnormal material the volume of lung available for expansion may be much reduced. Such lungs will also show a reduced volume increase for a given pressure change—that is, their compliance too will be reduced. In either of these last-mentioned circumstances the physical effort needed to produce a given degree of lung expansion (and hence of ventilation) will be increased; a reduced lung compliance will be associated with increased work of breathing (Read, 1961*a*).

The second functional disturbance is interference with gas diffusion across the alveolar-capillary membrane. In practical terms, the diffusion of oxygen only is affected; carbon dioxide is some 20 times as diffusible as oxygen and no thickening of alveolar walls compatible with life can appreciably interfere with transfer of carbon dioxide from capillary to alveolus. In the terminal portion of the alveolar capillary in the normal lung there is complete gas-tension equilibrium between gas and blood phases. In patients with thickened alveolar walls there may be a residual alveolar-capillary tension gradient for oxygen at the end of the pulmonary capillary of some 5, 10, 40 (or more) mm. of mercury. For example, if this end-capillary gradient were 30 mm. of mercury and the alveolar oxygen tension were 100 mm. of mercury, the end-capillary (and hence arterial) blood would have an oxygen tension of only 70 mm. of mercury, instead of the usual 100 mm.

On this basis, one would expect to find in the arterial blood of such patients a normal carbon-dioxide tension and a low oxygen tension and saturation. In fact, as represented in Figure I, there is no significant airway

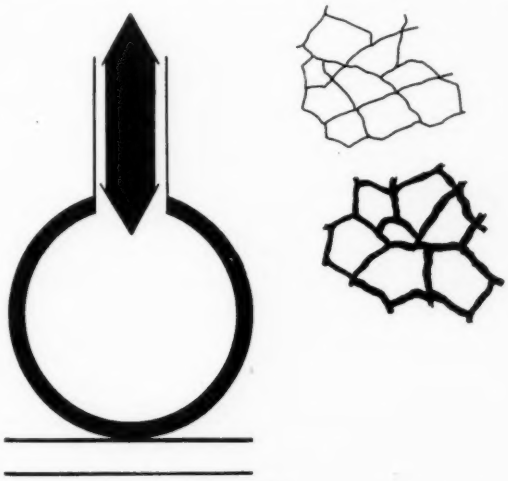

FIGURE I.
Diagrammatic representation of the functional disturbances in interstitial lung disease. Left: No airway obstruction. Hyperventilation. Barrier to free diffusion of gas from alveolus to capillary. Right: Thickening of the alveolar walls with increased rigidity of the lungs.

obstruction in the uncomplicated case, and these patients commonly hyperventilate even at rest. They wash out excess carbon dioxide, and often have an arterial blood carbon-dioxide tension lower than normal. The higher alveolar oxygen tension produced by the hyperventilation helps to compensate for the diffusion defect; if the end-capillary gradient remained 30 mm. of mercury, but the alveolar oxygen tension were raised to 120 mm. of mercury, end-capillary and arterial blood would have an oxygen tension of 90 mm. of mercury (not much reduced below normal).

However, in occasional patients, central cyanosis is seen at rest. This is commonly and glibly ascribed wholly to the diffusion defect with a resulting low oxygen tension in pulmonary capillary and arterial blood. Such an explanation is not very convincing. Suppose the patient hyperventilated only mildly, so that his alveolar oxygen tension rose only to 110 mm. of mercury, and that he had a very large end-capillary oxygen gradient of 40 mm. of mercury. The oxygen tension of his arterial blood would be 70 mm. of mercury, and this represents an oxygen saturation of 93%—well above cyanosis levels.

The answer to the problem lies in a third aspect of disordered respiratory function in these patients, clearly demonstrated by respiratory mass-spectrometer studies (Read and Williams, 1959). Although alveolar walls may be diffusely thickened throughout the lungs, the process may not be uniform in all areas. Some parts of the lungs may have a lower compliance than others; on inspiration such regions will expand less than the remainder, will receive less than their share of inspired gas, and will be, in effect, less well ventilated than the rest of the lungs (Figure II). Pulmonary capillary blood

[1] Presented at a plenary session of The Royal Australasian College of Physicians with the Australian Thoracic Society (formerly Laennec Society of Australia) in Sydney on October 12, 1960.

flow does not appear to be reduced in such regions, and the poor ventilation will be insufficient to oxygenate this blood adequately even in the absence of a diffusion defect. In the presence of the diffusion defect blood may leave such regions very desaturated. It is then the presence of local ventilation:blood-flow ratio disturbances superimposed on the general diffusion defect that accounts for the occasional example of central cyanosis at rest in patients with diffuse lung disease.

The diffusion defect is greatest in the group of patients with diffuse thickening of alveolar walls, and in patients with very diffuse nodulation of the alveolar walls. The compliance changes are likely to be greatest in these same two groups, and in the group with thickening of the interlobular septa.

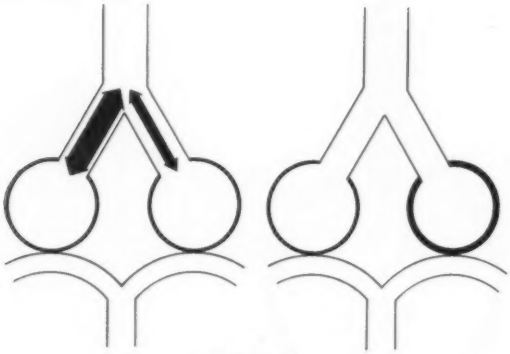

FIGURE II.

Diagrammatic representation of ventilation: blood flow ratio disturbances in patients with interstitial lung disease. Left: It is found that some regions of the lung (right-hand air-space) are less well ventilated than others (left-hand air space). Right: The likely mechanism for this phenomenon. The interstitial thickening is greater in relation to the right-hand air space, its compliance is less, and it expands less on inspiration. Blood flow remains uniform.

We use our knowledge of the disordered functional pattern in formal tests of respiratory function in such patients. These formal tests may be of considerable help to the clinician in a number of ways. In some cases they indicate the presence or otherwise of a diffuse lung lesion when all other evidence is equivocal. They allow objective assessment of the nature of the respiratory incapacity and its extent. Last, but not least, they provide an objective measurement of the efficacy of any therapy. They range from the most simple to the most highly complex. The simpler screening tests should be freely available in any clinic for the assessment and treatment of respiratory disorders. The more complex investigations require all the facilities of a well-equipped laboratory.

The simplest investigations are those related to the ventilatory function of the lungs. These require only a recording spirometer with a rapidly moving drum. We measure the vital capacity and the percentage of the vital capacity which can be forcibly expelled in the first second ($F.E.V._{\cdot1\cdot0}/V.C.\%$). In patients with lungs of low compliance one commonly finds a reduction of the vital capacity, but the $F.E.V._{\cdot1\cdot0}/V.C.$ ratio remains more than 70%. In emphysema (the most commonly confused lesion clinically) the vital capacity may be normal or low, but the $F.E.V._{\cdot1\cdot0}/V.C.$ ratio will be considerably reduced. The major limitation of these as screening tests for diffuse lung lesions lies in the wide range of normal values for vital capacity. The vital capacity cannot be regarded as certainly reduced unless it lies more than 20% below the predicted value for the subject.

Arterial blood may be collected anaerobically, following puncture of brachial or femoral artery under local infiltration anæsthesia and the carbon-dioxide tension and oxygen saturation of the arterial blood determined. One almost invariably finds a normal or low carbon-dioxide tension. The oxygen saturation usually lies within the normal range; occasionally it is a little reduced. In either event it sometimes falls on exercise, but our experience differs from that of some workers who find a fall of arterial oxygen saturation on exercise very commonly. For example, we do not share our Melbourne colleagues' views that a fall of arterial oxygen saturation on exercise represents a valuable sign of an interstitial lung lesion, because of the relative uncommonness of the finding. When 100% oxygen is breathed, the arterial oxygen saturation usually rises to normal levels, but in an occasional patient with some true arterio-venous shunting of blood within the lungs it fails to do so.

It is possible to measure the compliance of the lungs directly. The subject swallows a thin rubber balloon which lies in the lower part of his œsophagus, whence it transmits pressure changes via a thin "Polythene" tube to a sensitive measuring and recording device. The pressure changes in the lower part of the œsophagus closely reflect in turn the intrapleural pressure changes associated with respiration. If, at the same time, the subject breathes through a sensitive flow-head (which measures respiratory air flow) then we may collect all the data necessary for calculation of the compliance of the lungs. The information which a numerical expression of the compliance yields is similar to that which may be gained from a knowledge of the vital capacity. A knowledge of pressure and flow changes also allows us to calculate airway resistance directly. In the uncomplicated example of interstitial lung disease this will be quite normal.

Measurements of the compliance of the lungs suffer from the same disadvantage as measurements of the vital capacity. In both cases the range of normality is wide. If the initial compliance of the lungs is high, there will have to be a gross reduction before one can be sure of the presence of an abnormality. In following the progress of a single patient, of course, this objection no longer applies.

The most sensitive test for the presence of alveolar wall thickening is measurement of the diffusing capacity of the lungs. We are interested in the diffusion of oxygen, but for technical reasons it is more convenient to measure the diffusing capacity for carbon monoxide (D_{CO}). From this measurement we can infer how oxygen would behave. The subject inhales air to which a minute quantity of carbon monoxide has been added, and we measure the amount of carbon monoxide taken up in the lungs per minute and the partial-pressure difference of carbon monoxide between alveolar gas and pulmonary capillary blood. The D_{CO} is derived from the expression:

$$D_{CO} = \frac{\text{ml. CO taken up per minute}}{\text{mean alveolar-capillary CO tension difference}}$$

The result is expressed in units of millilitres per minute per millimetre of mercury. This measurement provides by far the most sensitive index of the presence and severity of an interstitial lung lesion. It will yield frankly abnormal results when the results of all the other tests are normal or equivocal. This does not imply that it detects the presence of disease which is insignificant or clinically unimportant. Rather does it indicate that the earlier tests are relatively blunt tools in dealing with this particular group of patients.

The main object of this exercise has been to draw attention to the functional disturbances which occur in diffuse lung disease, and to illustrate the means available for detecting them. It is rather more difficult to convince the unconverted of the value of these formal tests of respiratory function—perhaps a concluding case history may help.

A man, aged 32 years, an erstwhile footballer and deep-sea diver, began to experience shortness of breath. No reason could be found for this dyspnœa. There were no clinical signs of heart or lung disease, and an X-ray film of his chest revealed no abnormality (even when examined in retrospect). Tests of the ventilatory function of his lungs gave normal results. The oxygen saturation of his arterial blood was normal and did not fall on exercise. The compliance of his lungs was at the lower limit of

normal. Had investigation ceased at this point no diagnosis could possibly have been made. However, the D_{CO} was found to be 7 ml. per minute per millimetre of mercury — about one-third of the normal value. This allowed a confident diagnosis of interstitial lung disease to be made, and a lung biopsy was performed to elucidate the nature of the lesion; this proved to be a very severe diffuse interstitial pulmonary fibrosis.

One would not have dared suggest a lung biopsy without the clear-cut evidence of organic lung disease provided by measurement of the diffusing capacity of this patient's lungs. It is surely a reasonable conclusion that respiratory function tests are of considerable value for the greater understanding of individual diseases and of individual patients. There will still be those who will regard these tests in general as some sort of childish trick. But let us not forget that even Laennec's writings were described by his colleague, Broussais, as "a sublime romance, a fastidious collection of undigested facts or of useless discoveries".

Summary.

Diffuse lung disease may interfere with the distensibility of the lungs and with the transfer of gas across the alveolar-capillary membrane. One must invoke local disturbances of ventilation:blood-flow ratios to explain the occasional occurrence of central cyanosis at rest in such patients.

Formal tests of respiratory function may reveal (i) reduction of vital capacity, with an $F.E.V._{1\cdot0}/V.C.$ ratio which remains greater than 70%; (ii) normal or low arterial carbon-dioxide tensions; (iii) normal or occasionally reduced arterial oxygen saturations, which do not necessarily fall on exercise; (iv) reduced compliance of the lungs; (v) reduction of the D_{CO}, which is by far the most sensitive index of interstitial lung disease.

These tests are of major importance in diagnosis and in the assessment of disability.

Acknowledgements.

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PRIMARY ALDOSTERONISM WITH SEVERE HYPERTENSION RELIEVED BY ADRENALECTOMY.

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AND

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MUSCULAR WEAKNESS, polydipsia and polyuria have been the common presenting features of the published cases of primary aldosteronism (Conn's syndrome). Many patients have also had tetany. Usually high blood pressure has not been the dominant feature of the disease. We report here a case in which hypertension was the only clinical manifestation of aldosteronism; we are aware of only one other symptomless patient with this syndrome (Milne, Muehrcke and Aird, 1957).

Metabolic balance studies were performed on our patient while she was given a potassium load by mouth, as well as during the administration of one of the recently synthesized aldosterone antagonists (the steroidal spirolactone "SC 9420"[1] "Aldactone"); the study was continued after surgical removal of an adrenocortical adenoma. During the post-operative period she failed to retain a significant amount of potassium although the blood biochemical abnormalities were corrected completely.

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Clinical Record.

First Admission to Hospital.

Mrs. A., a married woman, aged 31 years, was first referred in March, 1954, to the Hallstrom Institute of Cardiology because of severe hypertension. Her father had suffered from high blood pressure and has since died from a ruptured aorta. Her mother, aged 67 years, and a brother, aged 33 years, were both alive and well, and were not hypertensive. There was no other history of cardiovascular or of endocrine disease in the family. The patient had three children, who were born in 1944, 1947 and 1949 respectively. Towards the end of her third pregnancy slight hypertension was noted, but she was given no special treatment and was confined normally. Thereafter she was normotensive and enjoyed good health until April, 1952, when she began to suffer from occipital headaches and bilious attacks. The headaches were present in the morning on waking, were unaccompanied by visual symptoms, and were relieved when she got up or took simple household analgesics. At about the same time she commenced to have bilious attacks, which started with feelings of nausea and terminated after one or two hours when she succeeded in vomiting small amounts of green, bitter-tasting fluid. Sometimes in association with the nausea, but at other times independently, she complained of tingling and numbness in both hands, especially the left, during which she was able to appreciate temperature, whereas the finer sensations were blunted. She said that her hands felt much the same as when a sphygmomanometer cuff had been compressing her arm for some minutes. All these symptoms had gradually increased in severity over two years. However, she had not been dyspnœic, her weight had been constant, her appetite was good, and she was able to carry out all her household duties. She denied menstrual irregularity, abnormal sweating, polydipsia, polyuria, loin pain and dysuria. She did not smoke and was practically teetotal.

On examination, Mrs. A. was 162 cm. in height and weighed 54·3 kg. She appeared to be a normally developed female, and unusual hairiness, obesity and striæ were all absent. The arteries to the limbs were not thickened, and repeated observations of the blood pressure while she was at bed rest were within the range 190 to 240 (systolic) and 135 to 150 (diastolic) mm. of mercury. The venous pressure was not elevated. The apex beat was forceful and left ventricular in type, being situated between the mid-clavicular and the anterior axillary lines in the fifth left intercostal space. No abnormality was found in the lungs, the abdomen or the ocular fundi. The urine contained no protein or reducing substance on repeated ward testing. The reaction was neutral or alkaline to litmus, and the maximum specific gravity after water deprivation was 1012. An electrocardiogram (Figure I) showed *S-T* segment depression, *Q-T* prolongation and prominence of the *U* wave, the *Q-T* ratio being 1·23. X-ray examination of the chest demonstrated widening of the aorta and concentric hypertrophy of the left ventricle. The hæmoglobin value, white cell count and erythrocyte sedimentation rate were all normal. The blood urea content was 29 mg. per 100 ml. The maximum concentration of urea in her urine after ingestion of 50 grammes of urea was 1·25 gm. per 100 ml. No abnormalities were discovered in an intravenous urogram or on microscopic examination of the urine; the urine was sterile. An intravenous phentolamine ("Regitine") test produced a negative result. Serum electrolyte determinations were not made. The diagnosis at this time was essential hypertension. The signficance of the hypokalæmic changes in the electrocardiogram

[1] Supplies of "SC 9420" were generously made available by Messrs. G. D. Searle & Co.

was not then appreciated. Mrs. A. returned to her home in the country with instructions to take pentolinium tartrate ("Ansolysen Retard") in a dosage of 20 mg. by injection twice daily, although even in hospital her blood pressure on this régime had shown wide fluctuations and there were pronounced side effects.

Second Admission.

The patient was referred back to the clinic in October, 1954, because she was seven weeks pregnant. Her doctor had found it necessary to reduce the "Ansolysen" to 12·5 mg. twice a day because of hypotensive episodes; however, her headaches and bilious episodes were much

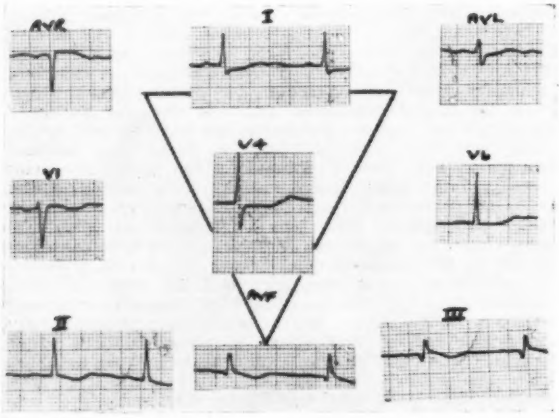

FIGURE I.
Electrocardiogram in March, 1954.

relieved. When she was examined, her standing blood pressure was 230/180 mm. of mercury, but in other respects the clinical findings were unchanged. The pregnancy was terminated and Mrs. A. returned to the country.

Third Admission.

In July, 1959, she was again examined at the clinic because she was six weeks pregnant. She was now taking "Ansolysen" by mouth in a dosage of 80 mg. three times a day, and no longer suffered from significant headaches, nausea or vomiting. Polydipsia, polyuria, muscular weakness, paralysis and tetany were still denied on direct questioning. Two hours after the morning dose of "Ansolysen" her standing blood pressure was 190/140 mm. of mercury, her fundi were normal and the findings on physical examination were the same as in 1954. Hypokalæmic changes in the electrocardiogram were less conspicuous, but a chest X-ray showed a definite increase in the size of her left ventricle. Her pregnancy was terminated, and she was then transferred to the Clinical Research Ward for further study.

In this ward, while she was at bed rest, and taking only "Raudixin" (50 mg. twice daily), her blood pressure was constantly 180/140 mm. of mercury. The results of the hæmatological and biochemical investigations are shown in Table I. Microscopic examination of the centrifuged urinary deposit showed 10 to 15 squamous epithelial cells and 0 to 2 leucocytes per dry field; there was no growth on culture. In a further electrocardiogram (Figure II), there was slight depression of the *S-T* segment (but still within normal limits), and the *T* waves were rounded and flat. The *Q-T* interval was still prolonged, the *Q-T* ratio measuring 1·19. The *U* wave was prominent, particularly in leads V_2 and V_3. In an intravenous urogram both kidneys appeared of normal size and excreted the dye without delay; the calyces on the left side did not fill well, but those on the right, as well as both renal pelves and ureters, were within normal limits. Perirenal insufflation was performed and clearly outlined a normal right kidney and right suprarenal gland; the upper pole of the left kidney and the region of the left suprarenal gland were not surrounded by air.

A series of metabolic investigations (*vide infra*) appeared to confirm the provisional diagnosis of Conn's syndrome; in view of the radiographic evidence of a

TABLE I.
Investigations Prior to Operation.

Test.	Result.
Hæmoglobin estimation	13·9 grammes per 100 ml.
Leucocyte count	5700 per cubic millimetre (normal distribution).
Platelet count	327,000 per cubic millimetre.
Urine:	
Albumin excretion	None detected.
Excretion of reducing substances	None detected.
pH	6·53
Sodium excretion	47 mEq per day.
Potassium excretion	61 mEq per day.
Water concentration test	Specific gravity 1012.
Endogenous creatinine clearance	95 ml. per minute.
Blood urea estimation	48 mg. per 100 ml.
Serum creatinine estimation	0·55 mg. per 100 ml.
Serum sodium estimation	140 to 146 mEq/l.
Serum potassium estimation	2·3 to 2·6 mEq/l.
Serum chloride estimation	93 to 96 mEq/l.
Serum bicarbonate estimation	27 to 35 mEq/l.
Serum calcium estimation	10·0 mg. per 100 ml.
Serum inorganic phosphate estimation	3·4 mg. per 100 ml.
Estimation of blood pH (arterial)	7·52
Estimation of carbon dioxide pressure (arterial)	42 mm.
Estimation of sodium-potassium ratio in saliva	0·1 to 0·4.

normal-sized right adrenal gland, it was thought that the adrenocortical adenoma was more likely to be found on the left side. After the patient had received two weeks of potassium supplement (75 mEq. daily by mouth

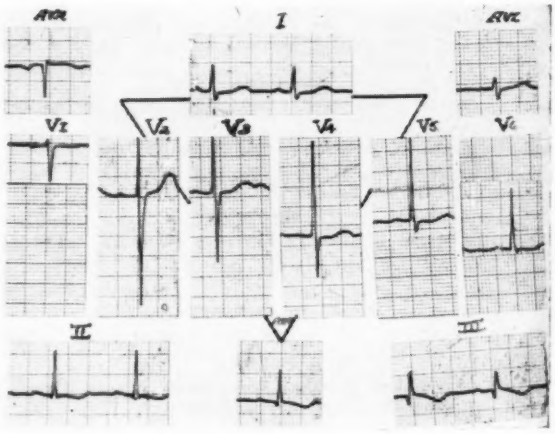

FIGURE II.
Electrocardiogram in October, 1959, prior to adrenalectomy.

as the chloride) and three days of cortisone acetate (100 mg. by intramuscular injection twice daily), Professor J. Loewenthal exposed the left suprarenal gland by an extraperitoneal approach through an antero-lateral skin incision. The gland was found to be enlarged by a single tumour approximately 2 cm. in diameter, and a complete left adrenalectomy was performed. There were no complications during or after the operation. The potassium supplement was suspended on the morning of operation, but was reinstituted on the seventh, eighth and ninth days afterwards. The cortisone was suspended

over six days, and the patient required two transfusions, each of 300 ml. of "packed cells", on the sixth and seventh days.

After the adrenalectomy, the blood pressure fell from 210/140 to 140/100 mm. of mercury, but then rose gradually until it was established at a fairly constant level of 165/125 mm. of mercury some six days later. Two days after operation the electrocardiogram showed multiple ventricular beats with some improvement in the *S-T* segment. The electrocardiogram was completely normal on the eleventh day, the *Q-T* ratio now being 1·095 (Figure III).

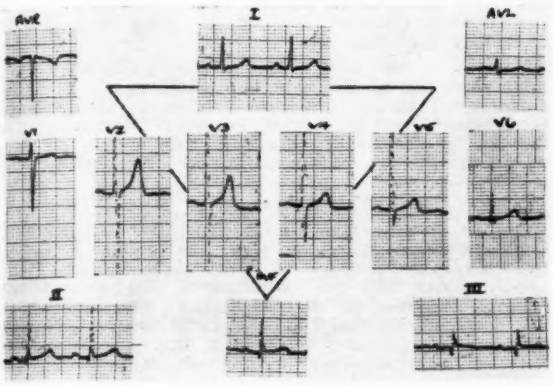

FIGURE III.
Electrocardiogram on the eleventh day after adrenalectomy.

The serum sodium concentration fell from a pre-operative level of 143 to 130 mEq/l. on the second day after operation, but had returned to 140 mEq/l. on the thirteenth day. The serum potassium concentration rose slowly until potassium was administered, when it increased sharply and eventually settled at 4·9 mEq/l. The serum bicarbonate content fell from 30 to 23 mEq/l. by the twelfth day after operation.

TABLE II.
Biochemical Changes following Adrenalectomy.

	Pre-Operative Figure.	Post-Operative Figure. 2 Weeks.	4 Weeks.	20 Weeks.	72 Weeks.
Blood urea content (mg. per 100 ml.)	48	60	54	46	40
Serum sodium content (mEq/l.) ..	145	140	135	143	137
Serum bicarbonate content (mEq/l.)	34	23	23	26	26
Serum potassium content (mEq/l.)	2·4	4·9	5·3	5·1	4·2
Blood pH (arterial)..	7·52	7·39	—	—	—
Endogenous creatinine clearance (ml. per min.)	95	—	—	85	70
Urine concentration test (S.G.) ..	1012	—	—	1013	1010
Salivary sodium-potassium ratio ..	0·1 to 0·4	—	—	0·5	—

The patient was discharged from hospital, fit and well, 13 days after operation, "Raudixin" therapy being recommenced in the same dose as before (50 mg. twice a day). In March, 1960 (20 weeks after adrenalectomy) her casual blood pressure was 150/110 mm. of mercury, and after a short period of rest it had fallen to 140/90 mm. of mercury. Her serum electrolyte contents were still normal, and the results of the other investigations are shown in Table II. A year later (March, 1961), her casual blood pressure (no therapy) was 160/110 mm. of mercury. The urine was acid, with a specific gravity of 1010, and the blood urea content was 40 mg. per 100 ml.

Dr. V. J. McGovern reported on the resected specimen (Figures IV and V)[1] as follows:

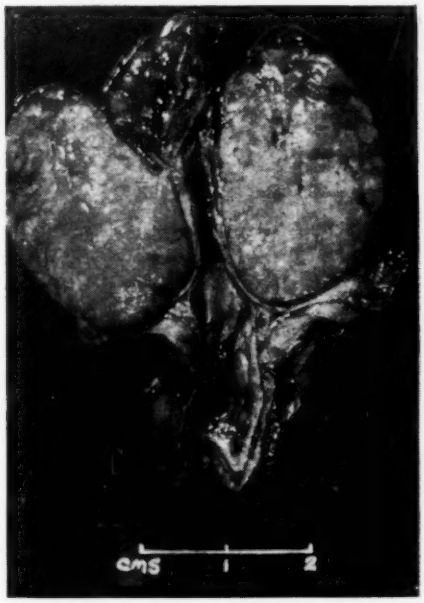

FIGURE IV.
Surgically removed left suprarenal gland, sectioned to show adrenocortical adenoma.

The suprarenal gland contains an adenomatous nodule measuring 2 × 1·5 × 0·3 cm. On section the tumour has a mottled red and yellow appearance. The tumour is composed predominantly of large cells of the type usually seen in the zona fasciculata. Many of these have large nuclei and some have more than one nucleus. There are also groups of small cells of the type seen in the zona glomerulosa; these are less numerous. There is no evidence of malignancy in this tumour.

The normal part of the suprarenal gland has a very narrow zona glomerulosa, but there are no other unusual features.

Metabolic Studies.

In the metabolic studies the patient was given a diet estimated to contain approximately 50 mEq of sodium and 50 mEq of potassium per day. All therapy was stopped. A sodium and potassium metabolic balance was carried out, carmine capsules being given by mouth in order to mark in the stools the beginning and the end of each three-day period. Serum electrolytes were determined usually every day, and saliva was collected in the mornings at 10 o'clock; paraffin was not used to assist salivation.

Duplicate diets (including fluids), dietary residues and stools were analysed in three-day periods. In each case the specimen was macerated with sufficient distilled water in a Waring blendor; a convenient aliquot of the homogenate was dried in an oven, ashed in a muffle furnace at 600° C., and dissolved in dilute nitric acid, and its sodium and potassium contents were estimated by flame photometry. The butter in the diet was analysed separately in the same way as described above, except that, after being dried, it was extracted with petroleum ether before being ashed in the furnace.

[1] See art-paper supplement.

The sodium and potassium contents of each twenty-four-hour specimen of urine were determined with a flame photometer; a small aliquot of each blood transfusion was laked with distilled water and then analysed similarly.

Effect of Aldosterone Antagonist.

Periods I, III and V were controls, during which no drugs were given. In period II the patient was given daily 400 mg. of the steroidal spirolactone "SC 9420", and in period IV this was increased to 1000 mg. per day.

In Figure VI are shown the results of serum electrolyte determinations, urinary sodium-potassium ratios and the over-all sodium and potassium balances; the last-mentioned results have been plotted so that a positive balance has been drawn above the base line and a negative balance below it. More detailed balance figures are given in Table III. It is clear that in the first control period the patient was "in balance" in respect of both sodium and potassium; administration of "SC 9420" in periods II and IV caused no significant change in the potassium balance, but the sodium balance reflected a small increase in the urinary excretion of this ion. The urine sodium-potassium ratio fell on each occasion on which the drug was administered. There were no significant variations in the salivary sodium-potassium ratio or in the serum sodium or potassium concentrations.

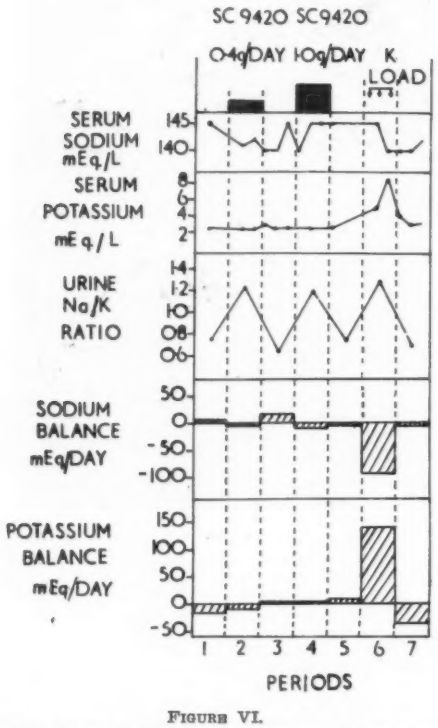

FIGURE VI.

Results of investigations prior to adrenalectomy (each period was of three days' duration).

Effect of Potassium Load.

The previous study was followed immediately by the administration of a potassium load (period VI); an extra 200 mEq of potassium were given orally each day as potassium chloride in thin gelatin capsules. Stool analyses confirmed that absorption of the salt was almost complete. The next three days (period VII) constituted a further control.

During potassium loading, the patient retained cumulatively 417 mEq of potassium, while she lost 282 mEq of sodium (Table III). The serum potassium level rose sharply to 8·6 mEq/l. (Figure VI). In the succeeding three days (period VII) the serum potassium level fell back rapidly to 2·8 mEq/l., and the patient lost a total of 108 mEq of potassium.

Post-Operative Balance.

Full balance studies were recommenced on the morning of the first day after operation, and were continued for 12 days. A potassium chloride supplement of 90 mEq per day was given on the seventh, eighth and ninth days; the patient was transfused with 300 ml. of packed cells on each day of the sixth and seventh days after operation.

Results of the serum sodium and potassium determinations and of the over-all sodium and potassium balances are shown in Figure VII, more detailed metabolic data being given in Table IV. The cumulative sodium and potassium balances at the end of 12 days were both negative, by 369 and 51 mEq respectively.

Discussion.

In the present case, the pre-operative diagnosis of Conn's syndrome was justified by the findings of hypertension, hypernatræmia, hypokalæmia, alkalosis and hyposthenuria, and was confirmed by the prompt and lasting correction of the biochemical abnormalities in the blood after removal of the adrenocortical adenoma. Unfortunately urinary aldosterone determinations could not be made, but they do not necessarily assist the diagnosis, since normal or only silghtly elevated values have been reported in several unquestionable cases of the syndrome (Chalmers *et alii*, 1956; Milne *et alii*, 1957; Russell *et alii*, 1957; Barrett *et alii*, 1959).

There are several unusual features worthy of comment. In the first place, during the period of study in 1959, the patient's serum potassium level varied between 2·0 and 2·7 mEq/l., yet she denied any symptoms, and in particular she admitted no muscular weakness, paralysis, tetany, increased thirst or polyuria. When her serum electrolyte levels had returned to normal after adrenalectomy she confirmed that subjectively she felt exactly the same as before operation. We are aware of only eight cases of Conn's syndrome in which muscle weakness or paralysis was not a significant complaint, and in seven of these, excessive thirst and polyuria were present and prompted further biochemical investigations (Tables V and VI). The remaining case was that of the second patient reported by the Hammersmith group (Milne *et alii*, 1957); she was aged 60 years and completely symptom-free, the diagnosis of primary aldosteronism being reached in the course of the routine assessment of a blood pressure of 180/110 mm. of mercury. It therefore appears that an occasional instance of this syndrome will not be recognized unless serum electrolyte determinations are performed on all hypertensive subjects.

The duration and severity of our patient's high blood pressure and her freedom from hypertensive complications are also of interest. From the history, it is likely that her blood pressure was elevated in 1952; certainly in 1954, when she was first examined, readings as high as 240/150 mm. of mercury were obtained while she was at bed rest. Hypotensive therapy was particularly unsuccessful, and it is probable that between 1954 and 1959 her diastolic pressure did not fall frequently below 140 mm. of mercury. Nevertheless, repeated examination of her ocular fundi revealed no pathological changes in the retinal vessels. Eleven days after adrenalectomy, the electrocardiogram was normal and showed no evidence of left ventricular strain.

The relatively benign nature of the hypertension in this patient is confirmed by our review of the literature of Conn's syndrome (Tables V and VI). Of a total of 32 cases of adenoma, the diastolic blood pressure regu-

TABLE III.
Pre-Operative Metabolic Balance Data.

Period.	Sodium (mEq per Day).				Potassium (mEq per Day).			
	Intake.	Urine.	Stool.	Balance.	Intake.	Urine.	Stool.	Balance.
I: Control	55	47	3	+5	55	61	11	−17
II: "SC 9420", 400 mg. per day	48	52	1	−5	41	42	9	−10
III: Control	48	29	3	+16	57	43	14	+1
IV: "SC 9420", 1000 mg. per day	49	57	2	−10	56	47	5	+3
V: Control	46	37	3	−6	68	46	15	+7
VI: Potassium load	43	133	5	−94	257	104	13	+139
VII: Control	47	53	2	−8	54	77	13	−36

larly exceeded 140 mm. of mercury in only five instances, and the hypertension was considered malignant in only one case, which was, however, also complicated by the presence of an atrophic left kidney. By contrast, all eight patients with Conn's syndrome due to bilateral adrenal hyperplasia had severe hypertension, and five of them were in the malignant phase with papillœdema.

During the early years of her illness, our patient suffered from numbness and paræsthesiæ in both hands; these symptoms were often associated with her bilious attacks, and completely disappeared after commencement of therapy for her hypertension in 1954. Their nature remains unexplained: they could have been caused by over-breathing while she was nauseated, or alternately they may have been due to incipient tetany. If the latter explanation is correct, it is difficult to understand why the paræsthesiæ never reccurred; however, from 1954 her dietary intake of sodium was moderately restricted, and it is known that the hypokalæmia of Conn's syndrome is less severe when sodium intake is low (Relman and Schwartz, 1957; Peterson, 1960).

The preliminary biochemical investigations performed on our patient demonstrated that, while there was pronounced extracellular hypokalæmia (2·4 mEq/l.), she continued to excrete approximately 70 mEq of potassium daily in her urine; other significant external loss of this ion was excluded. These findings were interpreted to mean that she suffered from either Conn's syndrome or primary potassium-losing renal disease. From Tables V and VI, it is obvious that hypokalæmia is an invariable feature of Conn's syndrome, but metabolic alkalosis and hypernatræmia are less constant. Loss of the power to concentrate and to acidify the urine is usually noted and inevitably raises the question of primary renal disease.

In our patient, hypernatræmia, metabolic alkalosis, normal glomerular filtration rate and low salivary sodium-potassium ratio were evidence in favour of Conn's syndrome. The repeated absence of even a trace of proteinuria is unusual in both conditions, as the hypokalæmia of primary aldosteronism usually causes secondary renal damage (the so-called hypokalæmic nephropathy).

In the attempt to obtain more evidence of the ætiological significance of aldosterone in our patient, she was given two courses of an aldosterone antagonist (the steroidal spirolactone "SC 9420"); drugs in this group act by antagonizing the peripheral action of aldosterone, but do not affect adrenal synthesis directly (Kagawa *et alii*, 1957; Liddle, 1957; Liddle, 1958). They have been used with some success to treat œdema in patients with secondary aldosteronism (Liddle, 1958; Kerr *et alii*, 1958; Slater *et alii*, 1959; Playoust and Blackburn, 1960).

In the present case, "SC 9420" caused a reduction in the urinary sodium-potassium ratio, but no significant alterations in the serum electrolyte concentrations, the salivary sodium-potassium ratio or the potassium balance. Most investigators have reported more dramatic changes in the serum electrolytes and in the sodium and potassium balances when spirolactone has been given to patients with Conn's syndrome, although occasionally there is an apparent resistance to the antagonist, and a large dose for a long period (for example, 2 grammes per day for 12 days) may be required (Salassa *et alii*, 1958; Bartter, 1960; Biglieri, 1960; Genest, 1960; Peterson, 1960; Simpson and Barnett, 1960). It is interesting that, in general, smaller amounts of spirolactone are necessary to treat subjects with secondary aldosteronism than those with Conn's syndrome, although urine aldosterone levels are usually much higher in the former cases.

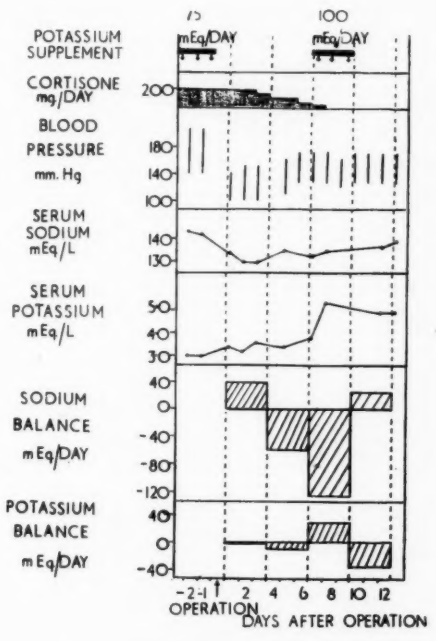

FIGURE VII.
Post-operative blood pressure recordings and biochemical data.

Leutscher (1956) and Ross (1959) in recent reviews doubted that Conn's syndrome was caused solely by increased production of aldosterone; they suggested that, in addition, there might be excessive secretion of another, as yet unrecognized, adrenocortical hormone (Ross *et alii*, 1959). In several reports there has been evidence

TABLE IV.

Post-Operative Metabolic Balance Data.

Post-Operative Days (Inclusive).	Sodium (mEq per Day).				Potassium (mEq per Day).			
	Intake.	Urine.	Stool.	Balance.	Intake.	Urine.	Stool.	Balance.
1st to 3rd	50	11	2	+37	54	47	8	−1
4th to 6th	44	102	2	−61	58	59	8	−9
7th to 9th	49	164	8	−123	153	111	13	+29
10th to 12th	42	13	5	+24	55	79	11	−36

of oversecretion of corticosterone with aldosterone (Mader and Iseri, 1955; Milne *et alii*, 1957, Case II; Peterson, 1960.)

One of the procedures recommended in the differentiation of Conn's syndrome from primary potassium-losing nephritis is the oral administration of a potassium load. In the first condition it was reported to be difficult to raise the serum potassium level to within the normal range, and the degree of potassium depletion (as indicated by the cumulative positive balance during the load) was less than would be expected from the severity of the hypokalæmia; at the conclusion of the supplement the balance immediately became negative, and the serum level rapidly fell to its previously low figure (Conn and Louis, 1955; Mader and Iseri, 1955; Milne *et alii*, 1957).

Our findings show that, contrary to the foregoing view, the serum potassium level in a patient with primary

TABLE V.

"Proven" Cases of Primary Aldosteronism, in which Surgical Removal of Adrenal Tissue was Followed by Symptomatic Relief and Biochemical Normality. (Case Reports until early 1960 only.)

Authors.	Patient's Age (Years) and Sex.	Duration of Symptoms (Years).	Blood Pressure (mm. of Mercury)	Symptoms.			Urine.		Plasma (mEq/l.).			Adrenal Abnormality.
				Polyuria.	Weakness or Paralysis.	Tetany.	Maximum Specific Gravity.	pH	Na^+	K^+	HCO_3^-	
Conn and Louis (1955)	34 : F.	7	175/105	+	+	+	1011	7·3	148	1·8	37	Adenoma.
Mader and Iseri (1955)	33 : F.	6/12	170/90	+	+	+	1014	6·5	143	1·6	43	Adenoma.
Chalmers *et alii* (1956)	43 : F.	3	220/150	+	+	+	1010	6·7	147	1·7	29	Adenoma.
Crane *et alii* (1956) ..	32 : M.	2	190/120	+	+	−	1027	?	152	2·1	40	Adenoma.
Eales and Linder (1956)	32 : F.	5	180/105	+	+	+	1010	6·6	143–156	2·6–4·2	31–38	Adenoma.
Hellem (1956)	46 : F.	4	150–230/ 100–115	+	+	+	1017	?	?	2·2	35	Adenoma.
Milne *et alii* (1957) :												
Case I	41 : F.	12	180/110	+	+	+	1010	Neutral	145	1·4	47	Adenoma.
Case II	60 : F.,	0	180/110	−	−	−	1016	?	145	2·0	40	Adenoma.
Hudson *et alii* (1957)	31 : F.	6/12	170–240/ 110–140	+	+	−[1]	1016	7·4	147	2·1	39	Adenoma.
Skanse *et alii* (1957) ..	45 : F.	5	220/120	+	+	−[1]	1011	7·2	144–152	2·3	23–29	Adenoma.
Hewlett *et alii* (1957) :												
Case I	44 : M.	5	220/128	+	+	−	1016	7·0	140–148	2·8	34	Adenoma.
Case II	63 : F.	5	170/100	+	+	−	1011	7·5	140–159	1·7	31	Adenoma.
Case III	43 : F.	2	220/120	+	+	−	1013	7·5	141–148	2·1–3·0	27–31	Adenoma.
Russell *et alii* (1957) ..	61 : F.	3	215/100	−	+	−	1012	6·2	150	2·2	33	Adenoma.
Nassim and Jory (1958)	40 : M.	7	High	+	+	?	Low	Neutral	144	2·6	?	Adenoma.
Crane *et alii* (1958) ..	43 : F.	4	170/100	+	+	−	1012	Slightly acid	135–149	2·1–3·1	25	Adenoma.
Siguier *et alii* (1958) ..	45 : F.	7	210/140	+	+	+	1016	6·5	135–143	2·4	27–33	Adenoma.
Bartter and Biglieri (1958) : Case II ..	27 : M.	1	260/160	+	−	−	1010	7·1	148	2·6	30–36	Adenoma.
Garlington and Bailey (1958) :												
Case I	44 : F.	3/12	210–230/ 115–140	?	+	?	?	?	?	Low	?	Adenoma.
Case II	34 : F.	? 6	200/130	?	+	?	?	?	?	Low	?	Adenoma.
Ortuzar *et alii* (1958)	27 : F.	5	170–230/ 100–120	+	+	+	1016	6·1	154	2·7–3·5	27–35	Adenoma.
Salassa *et alii* (1958) ..	49 : F.	?	High	?	?	?	Low	Alkaline	?	2·0	38	Adenoma.
Barrett *et alii* (1959) ..	47 : F.	2	130–220/ 90–160	+	+	−	1020	Neutral	135–150	2·6	23–34	Adenoma.
Orndahl *et alii* (1959) :												
Case I	15 : F.	3	200/150	+	−	−	1024	6·2	150	2·7	30	Adenoma.
Case II	28 : F.	2/12	195/115	+	+	+	1014	5·9	150	2·3	38	Adenoma.
Gabe *et alii* (1960) ..	43 : M.	5	240/140	+	+	−	1010	6·6	137–147	2·2–3·0	38	Adenoma.
Simpson and Barnett (1960)	37 : F.	7	240/135	+	+	−	1020	?	150	2·5	36	Adenoma.
Van Buchem *et alii* (1956)	17 : F.	15	200/130[2]	+	−	−	1016	6·9	143–150	1·7–2·8	25	Bilateral hyperplasia.
Fitzgerald *et alii* (1957)	31 : M.	1	220/135[2]	?	?	−	1028	7·0	141	2·7–3·2	34	Bilateral hyperplasia.
Kretchmer *et alii* (1957)	9 : M.	9	210/150	+	?	?	Low	?	?	Low	High	Bilateral hyperplasia.
Therian *et alii* (1958)[3]	15 : M.	5	230/140	+	−	−	1009	Alkaline	134–139	2·1–3·0	28	Bilateral hyperplasia.
Genest *et alii* (1960) ..	15 : F.	5	300/180[2]	+	+	+	1018	7·4	140	2·2–3·6	26	Bilateral hyperplasia.
Foye and Feichtmeir (1955)	60 : M.	8/12	200/135	+	+	−	1009	6·5	150	1·8	53	Carcinoma.
Holten and Petersen (1956)	13 : F.	2/12	200/150[2]	−	+	+	1018	Alkaline	125	2·9	32	Left gland normal.[4]
Bartter and Biglieri (1958) : Case I	13 : M.	13	160/120	+	−	−	1014		150	1·8–3·0	32	Normal.[5]

[1] Trousseau's sign present.

[2] Malignant phase.

[3] There was evidence in this case of over-secretion of other adrenal hormones besides aldosterone.

[4] Manifestations of hyperaldosteronism relieved by removal of left adrenal gland (histologically normal).

[5] Manifestations of hyperaldosteronism relieved by removal of one adrenal gland completely, and of four-fifths of the remaining gland (histologically normal).

TABLE VI.

Details of Probable Cases of Primary Aldosteronism.

Authors.	Patient's Age (Years) and Sex.	Duration of Symptoms (Years).	Blood Pressure (mm. of Mercury).	Symptoms.			Urine.		Electrolytes in Plasma (mEq/l.).			Adrenal Abnormality.
				Polyuria.	Weakness or Paralysis.	Tetany.	Maximum Specific Gravity.	pH.	Na^+.	K^+.	HCO_3^-	
Luft *et alii* (1951)	35 : F.	3	110–140/70–85	+	+	–	1011	?	147–156	2·9–3·5	?	Adenoma at autopsy.
Campbell *et alii* (1956)	39 : F.	3	210/110	+	+	–	1010	?	154	2·0	26	Adenoma at autopsy.
Brooks *et alii* (1957): Case III	52 : M.	15	240/170	+	–	–	1011	?	140	2·7	41	Adenoma at autopsy.
Fine *et alii* (1957)	33 : M.	4	250/100	–	+	–	1024	5·5	149	2·3	44	Adenoma at autopsy.
Hoet (1958)	54 : M.	1	270/160[1]	+	+	–	?	?	139	2·5	38	Adenoma at autopsy.[2]
Eales and Linder (1959)	47 : F.	2/12	300/160[1]	+	–	–	1014	5·5	131–146	2·7	29	Nodular hyperplasia at autopsy.
Wyngaarden *et alii* (1954)	46 : M.	1/12	245/160	+	+	–	1010	6·0	131	2·6	47	Bilateral hyperplasia at autopsy.
Hilton *et alii* (1959)	44 : M.	3/12	240/150[1]	–	+	–	1016	Alkaline.	142	2·7	35	Bilateral hyperplasia at autopsy.
Alsted and Halberg (1958)	43 : F.	2/12	140/110	+	+	–	Low	?	141	2·2	25	Normal at autopsy
Jackson and Oakley (1955)	34 : F.	1	210/130	–	+	–	1016	6·9	142	2·6	32	Not explored[3]
Sayers *et alii* (1955)	37 : F.	1	160/100	+	+	–	1010	?	148	2·3	30	Not explored[3]

[1] Malignant phase.

[2] Atrophied left kidney also found at autopsy.

[3] Maintained satisfactorily on oral potassium supplement.

aldosteronism may rise alarmingly during potassium loading. (The potassium intake of 257 mEq per day during this period was less than has been used by many investigators.) The result emphasizes the hazards of too rapid potassium repletion (Schwartz and Relman, 1953), as well as the unreliable nature of this response in the diagnosis of Conn's syndrome.

The other investigations which have been designed to distinguish the two conditions have not always been useful, and were not employed in this case. Most patients with Conn's syndrome (unlike those with primary renal disease) are able to conserve sodium efficiently while on a sodium-poor diet; but exceptions have been noted by Mader and Iseri (1955) and by Milne and co-workers (1957). Urinary aldosterone levels can also be misleading, as they may be normal in proven examples of primary aldosteronism, yet be increased in cases of chronic renal disease with secondary adrenal hyperplasia (Leutscher, 1956). Fortunately in many subjects with potassium-losing nephritis there are other factors in the history or in the routine examination which suggest the correct diagnosis — for instance, the very marked proteinuria and the radiographic demonstration of unilateral kidney disease in both cases described by Dollery *et alii* (1959). In some cases reported with the diagnosis of primary renal disease there was evidence at operation or autopsy of adrenocortical hyperplasia, and these are probably better described as Conn's syndrome (Wyngaarden *et alii*, 1954; Fitzgerald *et alii*, 1957; Eales and Linder, 1959). This distinction becomes exceedingly difficult when in one otherwise classical case of Conn's syndrome the patient had histologically normal adrenal glands (Bartter and Biglieri, 1958); the patient of Holten and Petersen (1956) is probably of the same type. However, despite its rarity, Conn's syndrome is much more common than potassium-losing nephritis, and in cases of doubt exploration seems justified.

The balance studies carried out on our patient after operation showed that there was no over-all potassium retention in the first 12 days, yet the serum potassium level rose rapidly from 3·0 to 4·9 mEq/l. Similar cases have been described by Eales and Linder (1956), by Relman and Schwartz (1957) and by Milne *et alii* (1957). It is probable that the potassium deficit in such patients was substantially corrected prior to surgery, and the continued pre-operative hypokalæmia was the result of a widespread effect of aldosterone on cell membrane permeability; a post-operative ion shift (or exchange) between intracellular and extracellular fluid compartments could therefore alter the serum concentration of potassium without any change in external balance.

The prognosis of this woman's hypertension appears to be good. At first it was thought that removal of an aldosteroma was followed by permanent reversion of the blood pressure to normal. However, as more patients were followed for longer periods of time, it became apparent that, at least in some instances, hypertension was not permanently relieved despite complete correction of the biochemical abnormality (Van Buchem *et alii*, 1956; Chalmers *et alii*, 1956; Milne *et alii*, 1957; Hewlett *et alii*, 1957; Skanse *et alii*, 1957). In our case, the blood pressure fell from 180/140 mm. of mercury (before adrenalectomy) to 170/125 mm. of mercury on the patient's discharge from hospital. When she was examined 20 weeks after operation, her basal blood pressure while she was taking 100 mg. of "Raudixin" daily was 140/90 mm. of mercury, and a year later it was 160/110 mm. of mercury, all treatment having been stopped.

Post-operative alterations in renal function have been variable in reported cases. Most frequently, the degree of proteinuria diminishes, and the results of tests of the kidney's ability to concentrate and acidify urine improve promptly. On the other hand, there may be pronounced and sometimes sustained impairment of the glomerular filtration rate and of the maximal tubular secretory capacity for "Diodrast" or para-aminohippuric acid (Chalmers *et alii*, 1956; Russell *et alii*, 1957; Relman and Schwartz, 1957; Milne *et alii*, 1957; Hewlett *et alii*, 1957). In our case there was a temporary rise in the fasting blood urea level shortly after adrenalectomy, but this later returned to its pre-operative concentration (Table II); we found no improvement in urine concentrating ability, or creatinine clearance.

Summary.

A case is described of primary aldosteronism due to adrenocortical adenoma. Severe hypertension resistant to hypotensive drugs was the main feature of the disease. Despite its severity, the hypertension was clinically benign, a finding which is characteristic of the great majority of cases of this disease. In this, as in one other reported case, muscular weakness, paralysis, tetany, polydipsia and polyuria were all absent. The laboratory findings included hypokalæmia, metabolic alkalosis, hypernatræmia and impairment of renal concentrating ability.

When an aldosterone antagonist ("SC 9420") was administered, there was a rise in the urinary sodium-potassium ratio, but neither the serum electrolyte concentrations nor the potassium balance altered significantly. Higher dosage might have caused greater changes. During three days of a high potassium intake (257 mEq per day), the cumulative retention of this ion was 417 mEq, and there was a concurrent loss of 282 mEq of sodium. On the last day of this period, the serum potassium level was 8·6 mEq/l. — an exceptionally high level for primary aldosteronism.

After surgical removal of an adrenal adenoma, the abnormalities of the serum electrolytes were promptly corrected; but metabolic balance studies showed that there was no potassium retention in the first 12 days after the operation. In an electrocardiogram the hypokalæmic changes disappeared completely in 13 days, and there was no evidence of left ventricular hypertrophy despite the long duration of the preceding hypertension.

The blood pressure fell gradually over the next five months, but had not reached normal levels one and a half years after operation; renal function did not alter significantly.

The unusual features of primary aldosteronism in this case and the differential diagnosis from primary potassium-losing renal disease are discussed.

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STUDIES ON POST-GASTRECTOMY MALABSORPTION: THE IMPORTANCE OF BACTERIAL CONTAMINATION OF THE UPPER SMALL INTESTINE.[1]

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SEVERE nutritional problems after gastrectomy are uncommon, but on the other hand weight loss of varying degrees has been frequently noted (Jordan, 1941; Muir, 1949; Everson, 1952; Zollinger and Ellison, 1954; Baron, 1954; Anderson *et alii*, 1955; Duthie, 1960). The two main causes for this are reduced food intake and malabsorption.

In order to study this problem we carried out fat-absorption studies on 59 patients, using ^{131}I-labelled glyceryl trioleate. Twenty-nine of these patients had had a gastric operation, and in the remaining 30 cases no operation had been performed and gastro-intestinal disease was absent. The majority of patients in the first group were below their pre-operative weight and some had been referred to us for investigation because of severe malnutrition and invalidism.

The use of isotopically tagged fats was introduced by Thannhauser and Stanley (1949), who used olive oil labelled with radioactive iodine (^{131}I). Since then glyceryl trioleate also labelled with ^{131}I has been utilized in the study of fat absorption, and many investigators have reported their findings in the literature. Studies of fat absorption after gastric surgery, using ^{131}I-labelled fats, have been made by Shingleton *et alii* (1956) and Ruffin *et alii* (1958). Playoust, Wyatt and Blackburn (1959) demonstrated the validity of the method by making simultaneous determinations of stool fat by chemical analysis.

Materials and Method.

The ^{131}I-labelled glyceryl trioleate was supplied by Abbott Laboratories through the Commonwealth X-ray and Radium Laboratory. The test dose, containing 50 μc. of labelled fat, was added to a mixture containing 50 ml. of water with milk powder and coffee essence and 2 ml. of stock emulsion. The emulsion was made up in the following proportions: 40 ml. of water, 40 ml. of olive oil and 2 ml. of gum acacia.

In order to prevent the uptake of ^{131}I by the thyroid gland, each subject was given 5 grains of potassium iodide thrice daily, starting on the day preceding the test and continuing for two days. The test dose of ^{131}I-labelled fat was given together with a standard breakfast containing 50 grammes of fat. The breakfast consisted of cereal with cream, two eggs, toast and butter, and was given at 9 a.m. on the day of the test.

Twelve millilitres of venous blood were collected at varying intervals, usually two, four and six hours after the test meal. Stools uncontaminated with urine were collected in tin containers for a period of three days, unless the patient was constipated, in which case the collection was continued until a sufficient specimen was obtained.

The radioactivity in the stools was measured by a scintillation counter placed external to the specimen. This was compared with a standard equal in radioactive strength to the administered dose and of similar geometry.

The blood samples were hæmolysed and 10 ml. aliquots counted in a scintillation counter and compared with an aliquot of a standard solution of radioactive sodium iodide which had the same strength as the administered material. The patient's blood volume was taken as 70 ml. per kilogram and the total circulating radioactivity was taken as the activity per millilitre of blood multiplied by the blood volume.

Results.

Normal Controls.

In the group of 30 patients in whom gastro-intestinal disease was absent none of the figures measuring stool radioactivity exceeded 3% of the administered dose and all the blood radioactivity levels were above 5% of the administered dose. In this regard our findings are in agreement with those of Playoust *et alii* (1959) and these figures have been taken as defining the normal limits of the results of this test.

Gastric Surgery without Malabsorption.

In a group of 11 patients on whom 12 tests were carried out, steatorrhœa could not be demonstrated. Two patients in this group had gastro-enterostomies without gastric resection, one had a Billroth I gastrectomy, and in the remaining eight cases a Billroth II procedure had been carried out. The results are shown in Figure I. It is seen that in this group the results lie within the normal range, both for blood and stool radioactivity.

Gastric Surgery with Malabsorption.

In a group of 18 patients on whom 26 tests were performed, the figures for stool radioactivity are all above 3%, indicating steatorrhœa (Figure II). Five of these had total or near-total gastrectomies, one patient had a Billroth I gastrectomy and in the remaining 12 cases a Billroth II operation had been carried out. On the whole the blood radioactivity levels have fallen in this group, many of them below the lower limit of normal. It can be seen that the blood levels, if taken alone, may not help in deciding whether or not a patient has malabsorption after gastrectomy, because they are a measure of the rate of absorption at a particular time rather than of the total absorption.

Causation of Post-Gastrectomy Malabsorption.

The various factors responsible for post-gastrectomy malabsorption have been studied by numerous investigators (Wells and Welbourn, 1951; Brain and Stammers, 1951; Kelly and Wangensteen, 1954; Lundh, 1957). It has been suggested that the loss of the gastric reservoir may lead to precipitate gastric emptying and increased intestinal transit time. This in turn may result in improper admixture of food with bile and pancreatic secretion. In addition, maldigestion may occur when food bypasses the duodenum, for under these circumstances the natural stimulus for pancreatic and biliary secretion is depressed. Paulley *et alii* (1957) and Joske and Blackwell (1959) have described histological changes in the small bowel mucosa in patients with post-gastrectomy steatorrhœa, and it has been suggested that the malabsorption may be

[1] Based on a paper read at a meeting of The Royal Australasian College of Physicians in May, 1960.

[2] Supported by a research grant from the Post-Graduate Medical Foundation.

related to a patchy atrophic jejunitis, but these observations have not been confirmed by other workers.

Finally an additional mechanism may be important. We believe that bacterial flora, operating under conditions suitable for their growth, can cause gross malabsorption after gastrectomy. It has been shown that the small intestine is normally sterile (Cregan and Hayward, 1953), but under certain circumstances it may be invaded by bacteria—for example, in gastro-colic fistula, multiple diverticulosis of the small bowel and the blind-loop syndrome. This in turn may lead to severe malabsorption,

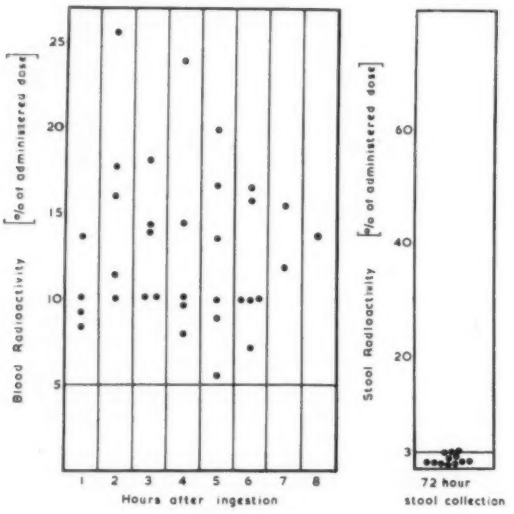

FIGURE I.
Normal radiotriolein absorption after gastrectomy.

with steatorrhœa, hypoproteinæmia, anæmia, electrolyte disturbances and vitamin deficiences. It occurred to us that a similar mechanism might be operating in some cases of post-gastrectomy malnutrition referred to us for study, because we noted that the afferent loop of the Billroth II anastomosis was a stagnant cul-de-sac thereby permitting bacteria to flourish within it (Kinsella and Hennessy, 1960). Ten patients with afferent-loop stasis have been observed and two are now described in detail.

Reports of Cases.

CASE I.—A woman, aged 43 years, had undergone a Pólya partial gastrectomy elsewhere for a large gastric ulcer in July, 1958. She remained well for two month; then she started vomiting and began to lose weight. There were also periodic bouts of diarrhœa. In December, 1958 a barium-meal examination revealed a large, dilated afferent loop which emptied very slowly. X-ray films taken at 12 hours and 17 hours showed barium scattered throughout the small bowel, but in both films there was still a considerable amount of barium in the dilated afferent loop (Figure III).[1]

In January, 1959, her legs became swollen and two months later, whilst holidaying in the country, she was admitted to hospital and told that she had pernicious anæmia. In May the hæmoglobin value was 9·6 grammes per 100 ml. Examination of the blood film revealed moderate anisocytosis only. Marrow biopsy showed normoblastic erythropoiesis and a normal marrow. A Schilling test indicated very poor absorption of vitamin B_{12}, only 1·7% of the test dose being excreted in the urine over a 24-hour period.

In June, 1959, admission to hospital became necessary because of persistent vomiting, diarrhœa and the loss of more than three stone in weight. It was noted that the vomitus always consisted of bile or a mixture of bile and food, and the stools were soft and clay-coloured. On examination she was an emaciated woman with pitting œdema of the upper and lower limbs and ascites. The hæmoglobin value was 11·1 grammes per 100 ml. and the blood film revealed a tendency towards macrocytosis. The total serum protein level was 4·0 grammes per 100 ml., the serum albumin level being 2·0 grammes per 100 ml. and the serum globulin level being 2·0 grammes per 100 ml. The fæcal fat excretion over a 48-hour period amounted to 18 grammes, a figure indicative of steatorrhœa. Treatment was instituted with a high-protein, low-fat diet, with added vitamins and folic acid. However, the patient discharged herself from hospital in July, but a week later she was readmitted with a fractured right femur and right humerus after a fall at home.

On her second admission to hospital she had severe wasting, with gross pitting œdema of the upper and lower limbs. X-ray films revealed a comminuted fracture of the head of the right humerus and a pertrochanteric fracture of the right femur. Although the patient was considered to be a poor operative risk, internal fixation of the right femur was carried out successfully on July 24. The hæmoglobin level after operation was 10·1 grammes per 100 ml. A fat-absorption test utilizing radiotriolein was carried out after chloromycetin had been administered

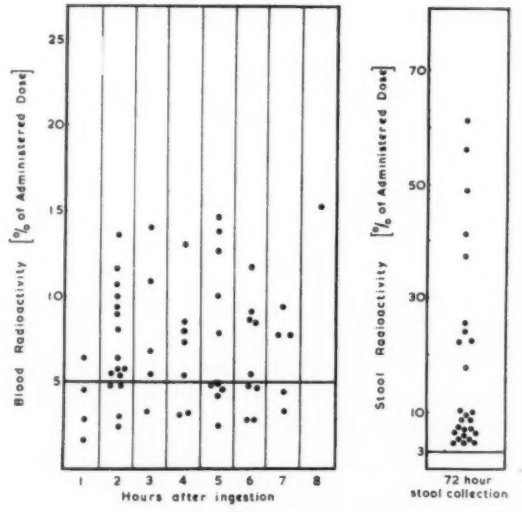

FIGURE II.
Abnormal radiotriolein absorption after gastrectomy.

in a dosage of 250 mg. six-hourly for four days. The fæcal radioactivity was only 1·2%, a figure indicating no abnormality in the fat absorption. The total serum protein level was 4·0 grammes per 100 ml.; the serum calcium level was 7·3 mg. per 100 ml., the serum phosphorus level was 2·8 mg. per 100 ml. and the serum alkaline phosphatase level was 14 King-Armstrong units. The Sulkowitch test on the urine on numerous occasions gave strongly positive results. A barium-meal X-ray examination at this stage revealed a vigorous to-and-fro pendulum movement of barium in a dilated afferent loop.

The œdema persisted in spite of treatment, which included a high-protein diet, folic acid, intramuscular injections of vitamin B_{12}, parenteral vitamin therapy and intravenous administration of albumin. From August 5 "Mersalyl" was administered on alternate days. Over the following two weeks a massive diuresis occurred and the œdema gradually disappeared. However, emaciation was even more apparent and occasional vomiting persisted. It was felt that recovery would not be complete without reconstruction of the gastrectomy, and this was undertaken elsewhere on September 1, 1959. At laparotomy a moderately thickened, dilated, writhing afferent loop was observed, while the efferent loop looked normal. The afferent loop appeared to be obstructed in the region of the stoma. During the operation the afferent loop was opened and found to contain dark, foul-smelling fluid. Splenectomy was performed and the gastro-jejunal anastomosis was eventually reconstituted.

[1] See art-paper supplement.

Culture of fluid taken from the afferent loop at operation revealed Gram-positive bacilli, a fairly heavy growth of two types of Friedländer's bacilli and *Staphylococcus albus*. Histological examination of the mucosa from the afferent and efferent loops revealed no abnormality.

Unfortunately, a gastric fistula developed and in spite of attempts to close this, the patient's condition slowly deteriorated and she died. Permission for autopsy was not obtained.

This patient had very marked stasis in the afferent loop. The malabsorption could not have been due to inadequate mixing of food with bile and pancreatic secretion or to loss of the normal secretin-pancreozymin mechanism, because all the barium, and presumably the food, entered the afferent loop first and then emptied slowly into the efferent loop. It seems likely that the hypoproteinæmia and steatorrhœa were due to a deficiency of pancreatic enzymes. Overgrowth of bacteria in the blind afferent loop was probably responsible because steatorrhœa could not be demonstrated after a course of chloromycetin.

CASE II.—A woman, aged 48 years, underwent cholecystectomy for gall-stones in 1952. In 1953, after attacks of upper abdominal pain, choledochoduodenostomy and sphincterotomy were performed, but the pains persisted. In 1957 chronic pancreatitis was suspected but serum amylase estimations, results of a glucose-tolerance test and a four-day fæcal fat analysis were normal. However, a barium-meal X-ray examination revealed a small lesser curve gastric ulcer. In June, 1957, a Billroth II partial gastrectomy was performed elsewhere. The common bile duct was explored, but no abnormality was detected. The pancreas appeared normal.

Progress was satisfactory till August, when diarrhœa commenced. The patient passed three to four loose, yellow, offensive motions daily and also experienced intermittent attacks of upper abdominal pain. Her appetite was poor and she could not tolerate milk or eggs. Within six months she had lost two stone in weight. In January, 1958, a fæcal fat analysis revealed steatorrhœa, 50 grammes of fat being excreted in the stools over a four-day period. Treatment was instituted with a low-fat, high-protein diet and added vitamins. There was temporary improvement and a radiotriolein absorption test in February gave normal results, the stool radioactivity being only 1·2%. However, in spite of various sedatives and antispasmodics, the patient continued to complain of severe weakness, recurrent upper abdominal pain and intermittent diarrhœa. Her weight remained stationary around 6 stone 12 lb. In September, 1958, a radiotriolein absorption test revealed frank steatorrhœa, the stool radioactivity being 25·4%.

In November, 1959, hospital admission was arranged for further investigation. A full blood count, the serum electrophoretic pattern, results of a glucose-tolerance test and *d*-xylose absorption were normal. A biopsy from the upper jejunum obtained with the Wood peroral suction tube revealed no abnormality. Contents aspirated from the upper jejunum were cultured for organisms. This revealed Friedländer's bacilli, non-hæmolytic streptococci and ***Bacillus proteus***.

On barium-meal X-ray examination the gastric remnant, stoma and efferent loop appeared normal. However, barium entered the distal one or two inches of the afferent loop, but was then sharply cut off; this suggested a kink or obstruction at this point (Figure IV).[1] In the hope of outlining the afferent loop, "Biligrafin" studies were done and by this technique definite dilatation of the afferent loop was demonstrated.

Radiotriolein absorption tests were carried out before and after a course of "Achromycin" (Figure V). The antibiotic was administered in a dosage of 250 mg. six-hourly for five days, commencing two days before the test. Subsequently subjective and objective improvement were noted. Only two bowel motions were passed daily and these were formed and of normal colour.

On February 2, 1960, laparotomy was performed. There were many adhesions and the liver was found adherent to the afferent loop and stoma. An anastomosis between the second part of the duodenum and the upper jejunal loop was performed. Fluid cultured from the afferent loop revealed a mixed flora, namely *B. proteus*, a coliform bacillus, Friedländer's bacillus and an anaerobic Gram-positive bacillus. Biopsies of the small-bowel mucosa obtained at operation revealed no abnormality. After the operation the patient's condition improved remarkably. Her pain disappeared and her appetite was excellent. For the first time since her gastrecomy she was able to eat normal meals. A fat-absorption test after the operation gave normal results (Figure V). The diarrhœa ceased, and by September she had gained 18 lb in weight.

This patient had a partially obstructed duodeno-jejunal segment which was demonstrated radiologically. The malabsorption was not due entirely to improper mixing of food with bile and pancreatic juice, because improvement was demonstrated after antibiotic therapy. It was concluded that bacterial contamination of the upper small intestine contributed to the malabsorption. After the duodeno-jejunostomy there was considerable increase in weight and the malabsorption disappeared. In this case the operation imposed little or no risk of stomal ulceration, because the patient was a female, the original ulcer was gastric and the gastrectomy was adequate.

Post-Gastrectomy Malabsorption without Radiological Abnormalities.

Not all patients with post-gastrectomy nutritional problems have demonstrable radiological abnormalities. In fact, in our experience X-ray films are often unrevealing. However, in spite of this, temporary improvement may occur after antibiotic administration.

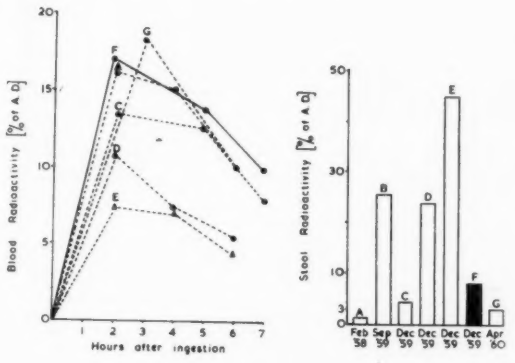

FIGURE V.

Post-gastrectomy malabsorption (Case II). Interrupted line with circles indicates absorption of radiotriolein. Interrupted line with triangles indicates absorption of radio-oleic acid. Uninterrupted line indicates absorption of radiotriolein after antibiotic administration.

In the patients we have studied, malabsorption appears to be most pronounced after total or near-total gastrectomy. Following radiotriolein absorption tests in these patients, the blood radioactivity curves tend to be low and the fæcal counts high. One of these patients suffered a rather unusual complication and the case will be described.

CASE III.—A man, aged 55 years, was found to have an extensive carcinoma of the stomach in August, 1957. In September total gastrectomy and resection of part of the head of the pancreas were carried out. An end-to-side anastomosis with jejuno-jejunostomy was performed. For three months after the gastrectomy he experienced diarrhœa, but subsequently his bowel motions were normal.

In December, 1957, a Schilling test revealed very poor absorption of vitamin B_{12}, only 6·7% of the test dose being excreted in the urine over a 24-hour period. On a low-fat, moderately high-protein diet with added vitamins, folic acid and fortnightly injections of vitamin B_{12}, he continued to improve, gradually put on weight and returned to work as a storeman. He remained well until May, 1959, when he was readmitted to hospital with acute intestinal obstruction. Chyliform fluid poured out at laparotomy and he was found to have a volvulus of the whole of the small intestine, which was dilated and blue with congested veins and lymphatics. The source of the obstruction was a band, which was divided; the volvulus was restored and immediately rubor returned to the bowel and peristalsis began.

[1] See art-paper supplement.

From that time on the patient suffered from severe diarrhœa, extreme weakness and weight loss. The diarrhœa persisted in spite of supportive therapy, which included folic acid and intramuscular injections of vitamin B_{12}.

In October, 1959, he was readmitted to hospital. A full blood count, the serum electrophoretic pattern and the results of a glucose-tolerance test were normal. After the oral administration of 25 grammes of *d*-xylose, only 1 gramme was excreted in a five-hour urine collection; this was indicative of malabsorption. A radiotriolein absorption test gave slightly abnormal results, the stool radioactivity being 5·4%. Barium and "Biligrafin" X-ray studies revealed no abnormality. A biopsy from the upper jejunum revealed normal villi. Culture of the jejunal aspirate resulted in a heavy growth of *B. proteus* and Friedländer's bacillus and a moderately heavy growth of *Streptococcus fæcalis*.

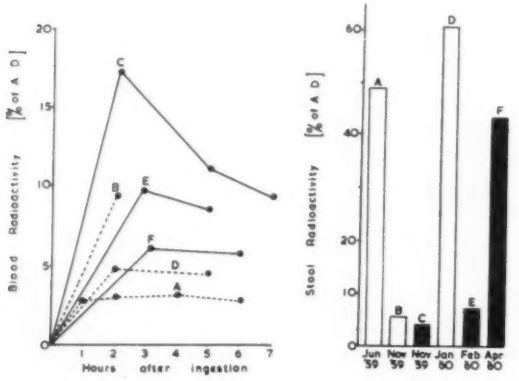

FIGURE VI.

Post-gastrectomy malabsorption (Case III). Interrupted line indicates absorption of radiotriolein. Uninterrupted line indicates absorption of radiotriolein after antibiotic administration.

It was decided to repeat the absorption tests after administration of an antibiotic. "Achromycin" was administered in a dose of 250 mg. six-hourly, but after three days this had to be suspended because of diarrhœa. Sulphaguanidine was then given for a further four days in a dose of 8 grammes daily. At the end of this period the radiotriolein and *d*-xylose absorption tests were repeated and improvement was noted (Figure VI and Table I).

TABLE 1.

Results of Radiotriolein and d-Xylose Absorption Tests in Case III.

	Radiotriolein Absorption.		*d*-Xylose in 5-Hour Urine (grammes).
	B.R.[1]	S.R.[2]	
Before chemotherapy	9·3%	5·4%	1
After chemotherapy	17·3%	4·1%	3

[1] Blood radioactivity at 2 hours, expressed as a percentage of the administered dose.

[2] Stool radioactivity over 3 days, expressed as a percentage of the administered dose.

After discharge from hospital in November, 1959 the patient remained well, was free from diarrhœa and put on weight. However, in January, 1960, the diarrhœa recurred and his fat absorption again became very abnormal (Figure VI). In February sulphaguanidine was recommenced with smaller dosage—actually 6 grammes daily, and this produced a favourable response. However, after an attempt to reduce the dose to four grammes daily in April, further deterioration in the fat absorption was noted (Figure VI). When last examined he was well and had one or two formed stools daily. Several attempts have been made to stop the sulphaguanidine therapy, but on each occasion the diarrhœa has recurred.

We concluded that the volvulus, by obstructing the circulation, had damaged the tissue of the small intestine, thus deranging its functions including its antibacterial mechanism, so that bacterial colonization occurred.

Discussion.

The potential danger from stagnant bowel contents associated with intestinal strictures, anastomoses and blind intestinal loops has been well recognized for many years. Faber (1895) suggested that the anæmia which accompanied intestinal stricture could result from absorption of a poison, and Meulengracht (1921) attributed it to bacterial infection above the stricture.

Various investigators have been able to produce anæmia and sometimes steatorrhœa in animals by creating intestinal strictures or blind intestinal loops. Thus Seyderhelm (1924) was able to produce anæmia in two out of 10 dogs after creating an intestinal stricture, and he demonstrated at autopsy a luxuriant growth of bacteria in the small bowel above the stricture. Cameron, Watson and Witts (1949) reported the successful production of macrocytic anæmia in rats by creating blind loops of small intestine. In one experiment in which the blind loop was designed to empty by peristalsis, macrocytic anæmia rarely occurred, and in fact "the anæmia developed only when there was some stenosis at the site of the anastomosis leading to dilatation and filling of part of the loop". In another experiment the blind loop was so arranged that peristalsis prevented it from emptying and the authors report: "A remarkable dilatation of the blind loop occurs. With an effective self-filling loop, all the animals die prematurely, some with and some without anæmia". Watson and Witts (1952) attributed the anæmia in their experimental rats to an alteration of the intestinal flora similar to that which occurs in cases of gastro-colic fistula in man.

In 1953 Siurala and Kaipainen reported two patients suffering from a blind-loop megaloblastic anæmia and they demonstrated a good response after treatment with a broad-spectrum antibiotic. Later on the blind loops were eliminated and the anæmia was cured. Halsted *et alii* (1956) described three cases of megaloblastic anæmia associated with intestinal lesions and they were able to demonstrate increased absorption of vitamin B_{12} after treatment with "Aureomycin" or "Achromycin".

In recent years the syndrome of intestinal diverticulosis with steatorrhœa and megaloblastic anæmia has been reported (Badenoch *et alii*, 1955; Krevans *et alii*, 1956; Scudamore *et alii*, 1958), and it has been suggested that stasis in the diverticula and alterations in the bacterial flora may be responsible, on the basis of improvement after antibiotic administration. Watkinson *et alii* (1959) described a case of massive jejunal diverticulosis with steatorrhœa, hypoproteinæmia and megaloblastic anæmia, which improved after excision of the diverticula.

Although glancing references have been made to the blind-loop mechanism in patients with post-gastrectomy steatorrhœa, some writers (Card, 1959; Bruce, 1959; Kay, 1960) have been sceptical about the importance of this mechanism. Card stated that although the afferent loop of a Pólya-type anastomosis is anatomically blind, stasis does not occur because "this particular piece of gut is extremely active, empties itself readily, and is normally washed through by pancreatic juice and bile after each meal".

However, we have studied 10 patients after Billroth II gastrectomy in whom the afferent loop did not empty readily, and the evidence suggests that these patients are in fact examples of the blind-loop syndrome. Two of them responded favourably to antibiotic therapy and subsequently at laparotomy an abnormal bacterial flora was cultured from the duodeno-jejunal loop. These observations have been supported by the work of Wirts *et alii* (1959) in America. Using ^{131}I-labelled triolein they were able to demonstrate improved fat absorption in four out of five patients suffering from post-gastrectomy (Billroth II) steatorrhœa, after the administration of tetracycline, and they cultured a heavy growth of bacteria from the afferent limb of two of their patients. They suggested that their cases were variants of the blind-loop syndrome.

Surgical Application.

To achieve consistently successful results from the Billroth II type of gastrectomy, surgeons should bear in mind the fundamental idea of "the quiet confluence of unobstructed streams", and they should purge from their minds the image shown in Figure VII*a*, unfortunately propagated in the literature and many textbooks, and replace it by the image shown in Figure VII*b*. The detailed methods of applying this second image to the actual operation have been described elsewhere (Kinsella and Hennessy, 1960). Their painstaking application in 400 patients has resulted in a minimal immediate mortality, there having been no deaths in the last 290 consecutive interval cases, and the late results have been excellent. The few patients whose weight has remained below their pre-operative weight have enjoyed good health with unimpaired working efficiency, and no patient has needed special investigation or reoperation for malabsorption.

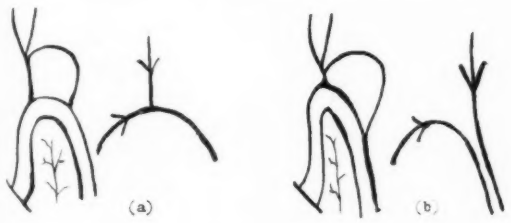

FIGURE VII.
a: Turbulence; *b*: confluence.

Summary.

Fat-absorption studies using ^{131}I-labelled glyceryl trioleate have been carried out on 59 patients. Gastric surgery had been performed on 29, and in 18 of these steatorrhœa was demonstrated.

The factors responsible for post-gastrectomy malabsorption are reviewed. The importance of stasis and bacterial contamination of the upper part of the small intestine is emphasized. Two patients illustrating this mechanism are described in detail.

The surgical application of these studies is discussed. Emphasis is placed on the fact that it is stasis, not precipitate emptying, which is to be feared and avoided.

An unusual case of malabsorption due to volvulus of the whole of the small intestine is recorded. In this patient a remarkable improvement followed treatment with sulphaguanidine.

Acknowledgement.

Figures III and IV are reproduced by courtesy of the editor of *The Lancet*.

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A PROMISING NEW DRUG FOR THE ELIMINATION OF HOOKWORMS.

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IN January, 1958, workers at the Wellcome Research Laboratories reported the synthesis of a new series of quaternary ammonium compounds which were lethal to nematodes in the gastro-intestinal tract of mammals (Copp *et alii*, 1958). Considerable activity was demonstrated against trichostrongyles in mice, rats and sheep and against hookworms in dogs and cats. Tests with labora-

tory animals, including monkeys, showed that the toxicity of these salts was low. The less soluble salts were poorly absorbed when given to human volunteers (Rogers, 1958). The new compounds were given the generic name bephenium.

Clinical trials were made, and reports of the value of the new drug in the treatment of hookworm disease in man appeared by the end of 1958 (Goodwin *et alii*, 1958). The authors compared the efficacy of bephenium salts with that of tetrachlorethylene in the treatment of 284 persons infected with *Necator americanus* in Ceylon. They selected bephenium hydroxynaphthoate ("Alcopar") as the most suitable salt, and stated that a single dose of 2 or 3 grammes of the base, or multiple doses on the same or successive days, all gave results which compared favourably with those obtained with tetrachlorethylene. The new drug proved particularly useful in the treatment of cases of severe anæmia, because of the absence of toxic side effects. Young *et alii* (1958) reported that bephenium chloride was more effective than tetrachlorethylene in eliminating *Necator americanus* from the inmates of a mental hospital in South Carolina.

More recently reports have appeared on its efficacy in dislodging *Ancylostoma duodenale*, usually a more difficult parasite to get rid of than *N. americanus*. Nagaty and Rifaat (1959) reported excellent results in an out-patient clinic in Egypt, 5 grammes of "Alcopar" being given in a single dose in the middle of the morning to 239 patients. No side effects were observed, and 95% of the patients were said to have been cleared. This figure seems to be based on a single stool examination, and must be accepted with reserve. Ahmad and Rasool (1959) in West Pakistan gave 5 grammes of "Alcopar" on an empty stomach, withheld food for three hours and gave a saline purge. They reported 82% clearance after the first dose and 93% after the second, compared with 18% and 20% after tetrachlorethylene administration.

Hookworm infection, mostly due to *A. duodenale*, is still a major problem in mental hospitals and aboriginal settlements in Queensland, and treatment by any of the standard methods has given discouraging results. It was therefore decided to try this new drug.

Methods.

"Alcopar" is supplied in the form of greenish-yellow granules with a slightly bitter taste. It was given mixed with water, or with syrup and water to disguise the bitterness. In the earlier trials, the first dose was given on an empty stomach before breakfast, and subsequent doses were given at mid-morning and mid-afternoon. Later it was found that a single dose given at 10 a.m. gave, if anything, slightly better results than one given at 6 a.m., and treatment is now given at mid-morning. Purgatives were not given, except in a few special cases, and food was not withheld.

Assessment of the results was made by the examination of stools by Willis' salt flotation method, the specimens being obtained at approximately weekly intervals. The patients in a mental hospital were not regarded as cured until at least three clear specimens were examined, but this standard could not be maintained at the aboriginal settlements.

Trials at a Mental Hospital.

Samples of "Alcopar" were received in 1959, and adult male patients with moderately heavy infections were selected for treatment. Some of them had been treated repeatedly with tetrachlorethylene or hexylresorcinol without any apparent effect on their worm burden. Of 15 men given three doses each of 5 grammes on the one day, eight were cured; three were given a second course, and all were cured. The others could not be treated again at this time, as no more drug was available.

When further supplies of "Alcopar" were received, patients were treated as a routine with a single dose, since the three-dose régime was expensive. The results of treating 25 men with 5 grammes of "Alcopar" are set out in Table I, and compared with the results obtained previously with tetrachlorethylene and hexylresorcinol. A statistical analysis was made of these figures and it was reported that the results with "Alcopar" were significantly superior to the others at all stages, except for the comparison between "Alcopar" and hexylresorcinol after the first treatment, for which P lay between 0·05 and 0·10. Differences between the results for tetrachlorethylene and hexylresorcinol were not significant at any stage.

Boys aged from 6 to 16 years were given the same dosage of "Alcopar" as the men, 13 out of 23 being cured by the first course. The subsequent history of those who were not cured by the first dose is not easily set out, as different régimes were used. The impression was gained that the three-dose régime did not greatly improve the result, as a few boys required several courses, and one boy was still infected, albeit lightly, after seven courses (five single doses and two three-dose courses spread over six months). After the eighth course (one dose), he appears to be free from hookworm. This was a persistent infection, and not due to reinfection, as the child was confined to a hospital ward.

TABLE I.

Comparison of Three Drugs Used in the Treatment of Hookworm in Mental Hospital Patients.

Drug.	Number of Courses.	Number of Patients Treated.	Number Cured.	Approximate Progress've Percentage Cured.
"Alcopar" (5 grammes)	1	25	19	75
	2	6	4	90
	3	2	2	100
Tetrachlorethylene (4 ml.)	1	16	4	25
	2	12	1	30
	3	11	1	40
Hexylresorcinol (1 gramme)	1	14	6	40
	2	8	2	60
	3	6	2	70

Adult hookworms were not examined from these patients, but third-stage larvæ obtained by culturing fæces were identified as *A. duodenale*.

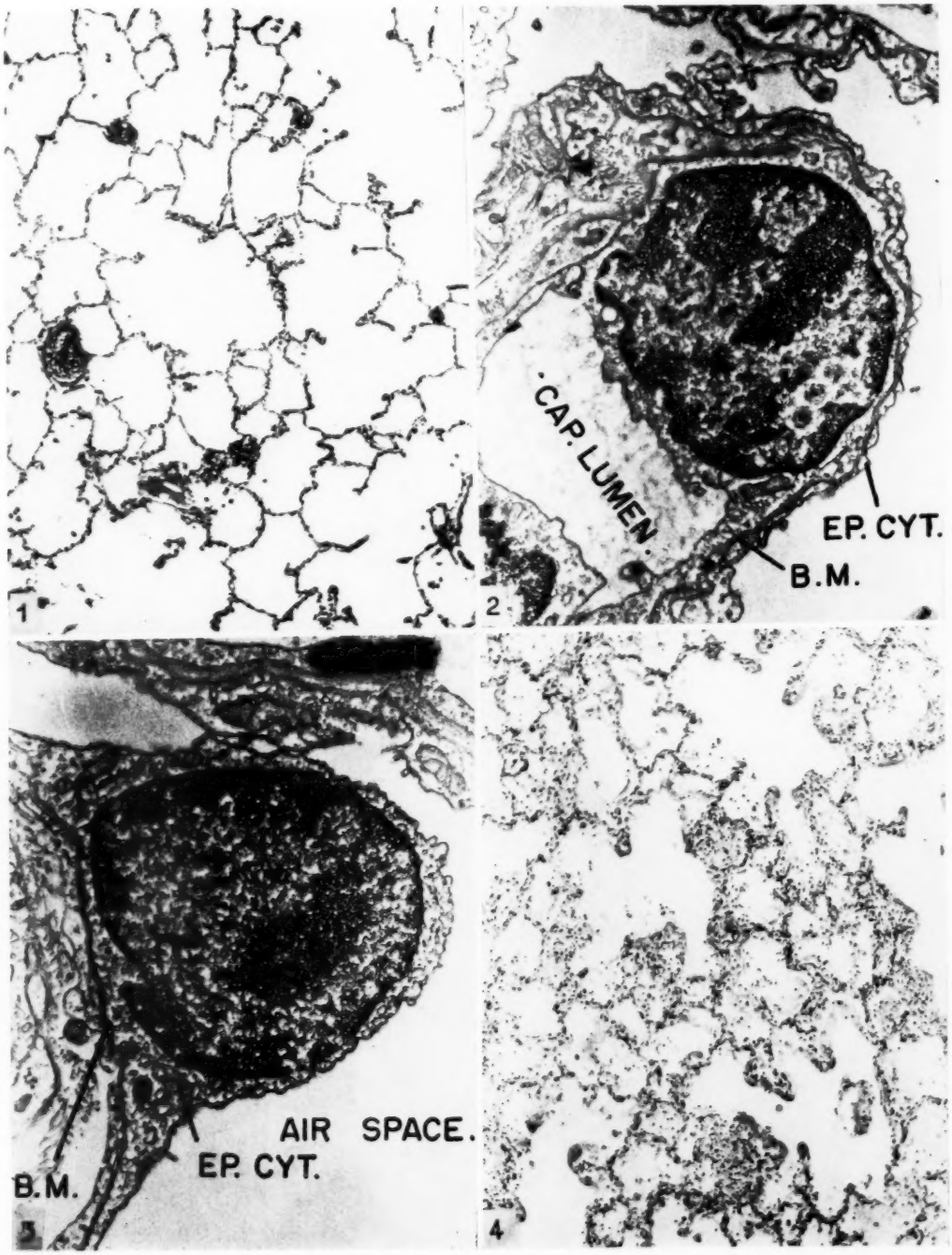
Trials at Mornington Island Mission.

Hookworm has been a major problem at this mission for many years. Mass treatment with tetrachlorethylene has been given regularly at three-monthly intervals, with very discouraging results. In June-July, 1959, all the school children were found to be infected, many heavily. Infection was almost universal in the pre-school children aged from about one year upwards. Many adults were heavily infected.

Samples of "Alcopar" were used in some preliminary trials. Adults and older children were given 5 grammes, but it was thought prudent to divide the dose for small, underweight, and anæmic children. As 2·5 grammes were found to have no effect on the worm burden, three doses of this amount were given, one before breakfast, one at mid-morning, and one at mid-afternoon. Four heavily-infected children aged from three to six years were subjected to this régime and watched carefully. No ill-effects were observed. Three of them were regarded as cured, the fæces being free from hookworm ova on two occasions during the following three weeks; the fourth child was still passing a small number of ova at the second examination. All the worms collected from the fæces proved to be *A. duodenale*.

As soon as a regular supply of "Alcopar" became available, all infected persons were treated, and retreated when necessary, by the sister in charge, who also checked the results by microscopic examination of the stools. Some children with heavy, persistent infections were kept in hospital on a low-residue diet for two days before treatment, which was then usually successful. Only two children out of over 150 treated consistently vomited the drug. No other ill effects were noted. There has been

ILLUSTRATIONS TO THE ARTICLE BY K. VINER SMITH.



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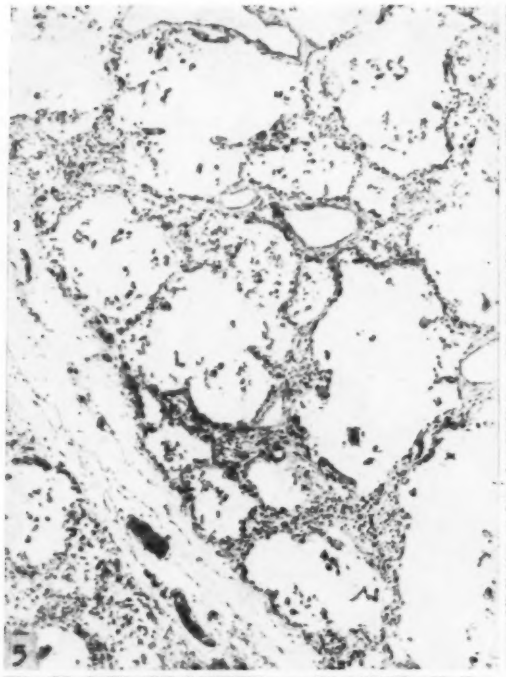

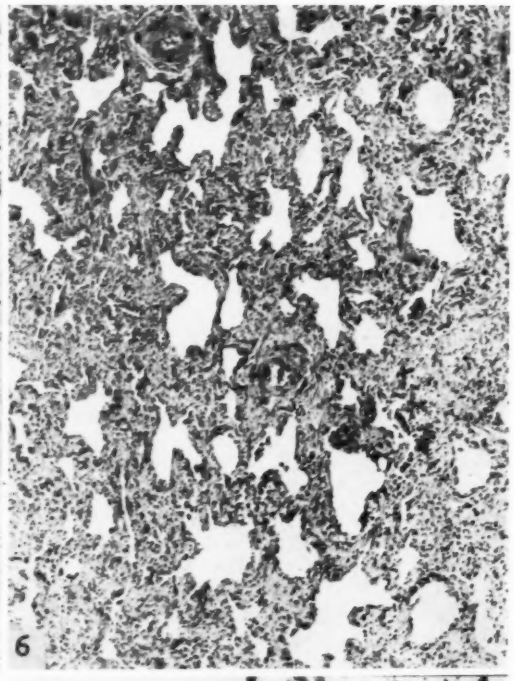

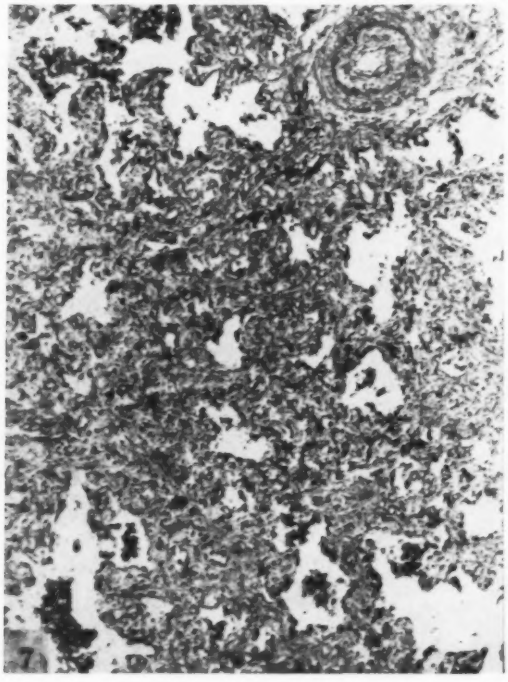

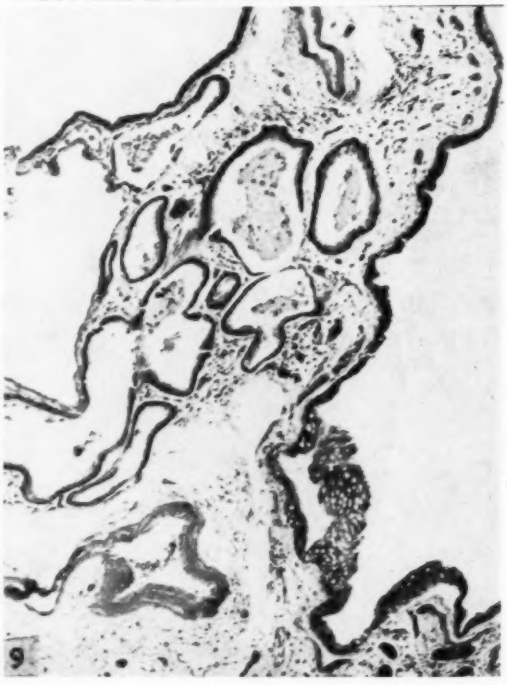

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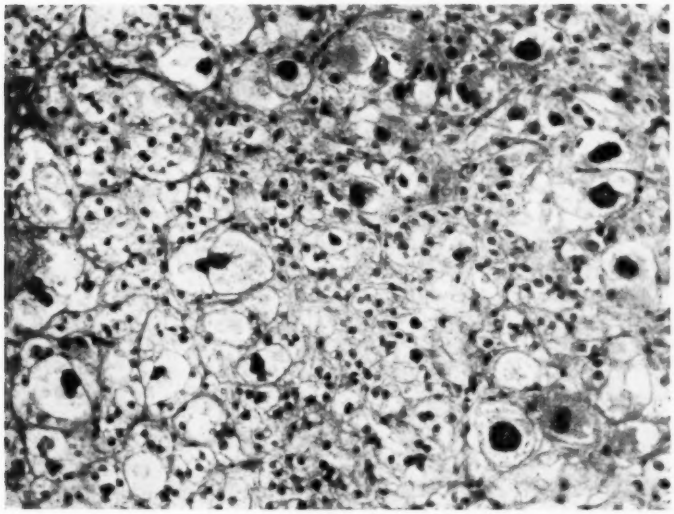

FIGURE V.
Microscopic appearance of the adrenocortical adenoma (see text). (Hæmatoxylin and eosin stain.)

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FIGURE III.
Barium study of alimentary tract (Case I). Twelve hours after the meal a considerable amount of barium is seen in the dilated afferent loop. Barium is also scattered throughout the small bowel.

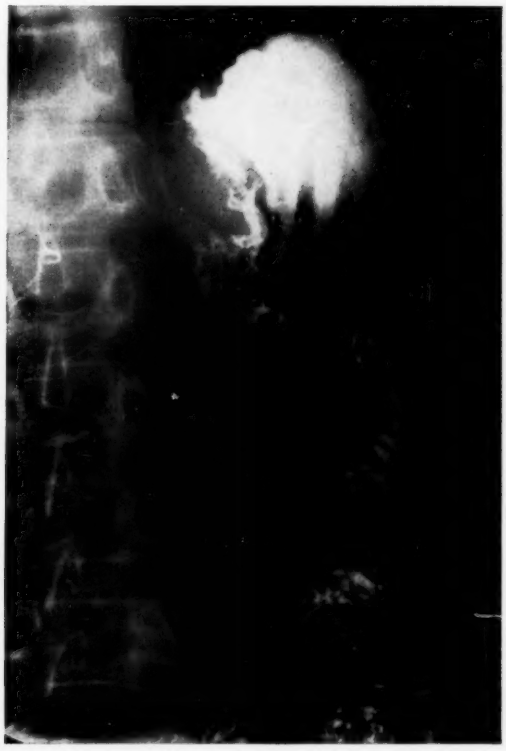

FIGURE IV.
Barium study of alimentary tract (Case II). Barium has entered the distal one or two inches of the afferent loop, but is then sharply cut off; this suggests a kink or obstruction at this point.

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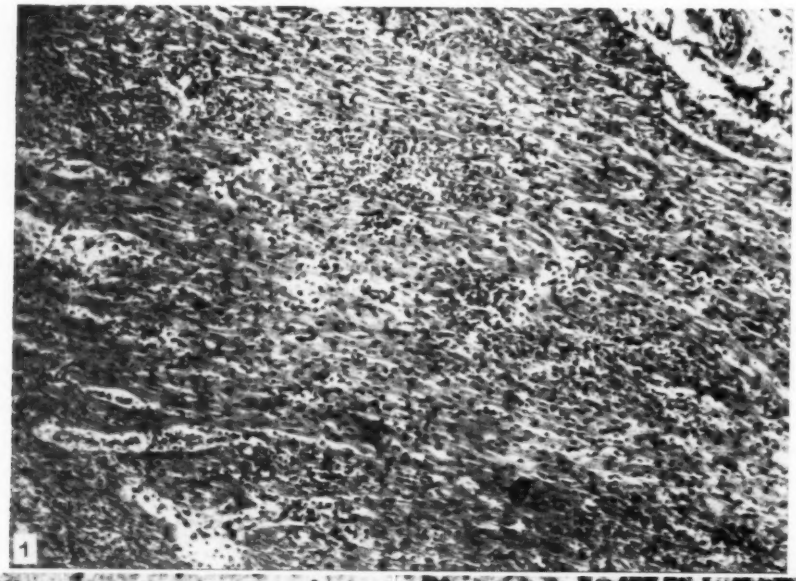

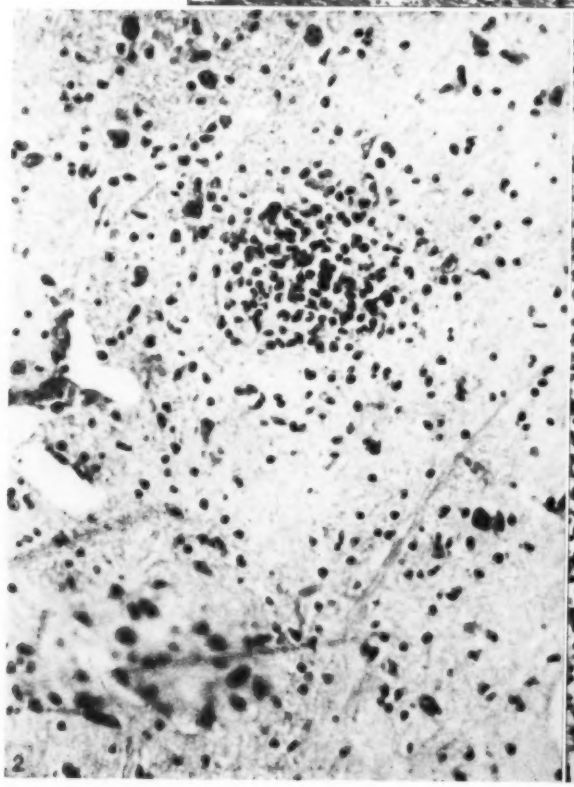

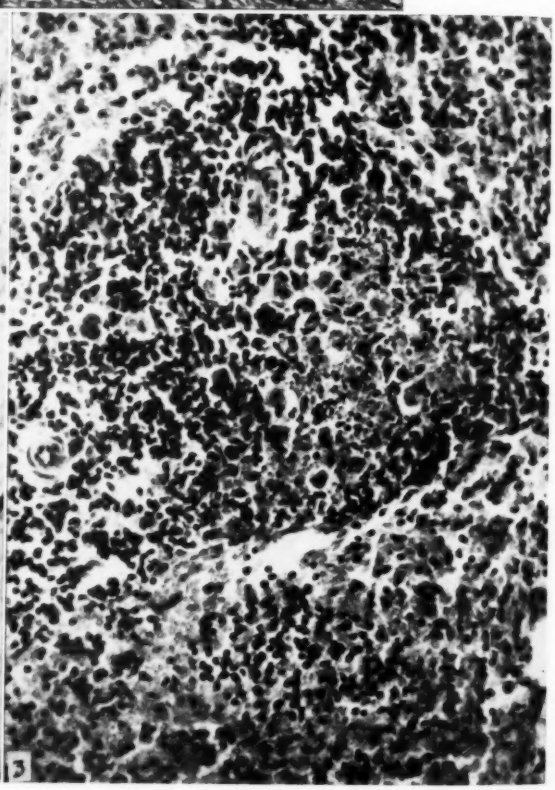

a steady reduction both in the infection rate and in the intensity of infection. At the same time, a definite improvement in sanitation has been brought about by the building of a large number of new, hygienically constructed lavatories. However, there is clear evidence that reinfection took place, even during the dry season, when the soil around the dwellings appeared to be too dry for larval development.

In order to assess the present infection rate, two batches of formalinized fæces were sent to Brisbane in September and December, 1960. In this way, 47 children were examined twice, and 85 on one occasion. Of those examined twice, 17 showed hookworm ova in the fæces on one or other occasion, and the remainder appeared to be free on both occasions. Of those examined once, 13 showed hookworm ova. The majority of the infections seen were quite scanty.

Trial at the Mitchell River Mission.

The infection rate in children was found to be 43% in March-April, 1960. Infected children were given a single dose of 5 grammes before breakfast, or three half doses, totalling 7·5 grammes, spread over the day. Some small children were inadequately treated, as they were not brought back for their second or third dose. Specimens of fæces taken one to two weeks after treatment were formalinized by members of the mission staff and sent to Brisbane for checking. Of 36 specimens submitted in this way, only two showed the presence of hookworm ova, so that there appears to have been a considerable reduction in infection rate.

Discussion.

The reason why the drug sometimes fails is obscure, but the observation of Burrows (1958) may throw light on these puzzling cases. He treated dogs infected with *A. caninum* with salts of bephenium, collected all the worms passed, and later examined at autopsy all the animals and counted the surviving worms. He found that 97% of the worms had been removed, and that those which survived were attached to the mucosa one-third to one-half of the intestinal length from the pylorus, instead of in the normal position in the duodenum. It is possible that something similar may occur in man, and that a preliminary period on a low-residue diet is consequently useful in treating these cases.

Side effects have been very few, only occasional children consistently vomiting the drug. This is in contrast to the unfavourable report recently published by Jung and McCroan (1960), who found that "Alcopara" [*sic*] was less efficient than tetrachlorethylene in the treatment of white children attending elementary schools in Georgia, and that nausea and vomiting were frequently complained of. However, no attempt was made, apparently, to disguise the bitter taste. They also gave larger doses (maximum 5 ml.) of tetrachlorethylene than are given here (maximum 4 ml.), and they were presumably dealing with *N. americanus*, which is known to be more susceptible to tetrachlorethylene than is *A. duodenale*.

Conclusions.

"Alcopar" has proved considerably more efficacious than either tetrachlorethylene or hexylresorcinol in the treatment of persons infected with *A. duodenale*.

It is easier to administer than either of the other drugs, and is free from the unpleasant side effects of tetrachlorethylene.

Acknowledgements.

I wish to thank Dr. R. A. Atherton and Dr. D. H. Lock for their cooperation; Dr. K. Severin Alstad, Medical Director of Burroughs Wellcome and Co. (Australia) Ltd., Sydney, for the trial consignments of "Alcopar"; and Dr. H. Silverstone for the statistical analysis. I am grateful to the staffs of the Mitchell River Mission and the Mornington Island Mission for their hospitality and cooperation, particularly Sister Rosemary Yappa, who has allowed me to see her records, and has sent preserved fæces for examination.

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OPERATIVE TREATMENT OF VARICOSE VEINS.

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VERY conflicting views are held by patients regarding the scope and success of operations for varicose veins. This must reflect not only similar uncertainty in the minds of their medical advisers, but also an often justifiable reflection on the operative treatment given. It is still too often that inadequate operations are performed, and too many attempts made to correct these by injections—procedures that are doomed to failure. No wonder that patients are sceptical, disillusioned and reluctant to undergo surgical measures designed to relieve their disease.

Very little is known of the natural history of varicose veins. We are ignorant of their ætiology or why certain veins are affected more often than others. We are quite unable to predict the course of the condition in any individual patient if he is seen at an early stage, although prognosis is easier at an advanced stage—a stage at which it is unfortunately too often seen. Symptoms complained of can often not be correlated with the physical extent and the apparent severity. Nevertheless we can define certain types of the disease and know that in the majority of patients the condition is unrelentingly progressive in extent and extension, as well as in the severity of affected veins. However, the rate of progression is variable, ranging from slow deterioration over many years to rapid progression and the onset of complications—particularly ulceration, which is often the compelling reason why treatment is sought.

It is common experience that while often no complete cure can be effected, the condition can be kept well under control and complications entirely prevented. It is quite erroneous to assume that (i) any standard operation performed irrespective of condition of the leg, or (ii) any operation at all is going to cure the condition permanently. An operation planned to suit the condition presented by the patient is but the beginning of a course of treatment which consists of (i) eradication of remaining radicles, (ii) regular, life-long follow-up and revisionary treatments as found necessary in the light of these follow-up examinations. It is essential to explain this to the patient and obtain his understanding and cooperation. It is our responsibility to organize this follow-up service and not to rely on vague instructions to return.

The symptoms of varicose veins are manifold and diverse, but those most commonly complained of are: (i) aches and pains in the legs and feet; (ii) swelling of

the ankles and the feet—especially towards the end of the day; (iii) nocturnal cramps; (iv) itching; (v) dermatitis; (vi) eczema; (vii) varicose pigmentation; and finally (viii) ulceration, with its own attendant sequels of pain, stiffness and unfortunately only too often reduced activity. Bursting sensations in the leg or around the ankle are symptoms of deep venous valvular incompetence and may reflect a previous deep thrombophlebitis. However, treatment is sought not only on account of these symptoms, but often because of the cosmetic disfigurement of varicosities.

If other causes of symptoms have been satisfactorily excluded, then treatment should be undertaken without prevarication and according to a definite plan. Conditions to be excluded are not only the general or local diseases likely to cause œdema, but also arterial insufficiency and local orthopædic conditions as possible causes of pain. A pelvic tumour must in all cases be excluded. General physical examination of the patient should complement a detailed local examination of the leg.

When the diagnosis has been made, a planned course of treatment is begun, for we can with certainty offer our patients relief. We should not dismiss their complaints as minor and not worthy of our attention. Prolonged ache or pain, or for that matter any chronic discomfort, is difficult to "grin and bear", particularly when relief is possible and certain.

Treatment is directed either towards relief of the symptoms by a supportive stocking or operative eradication of the disease. Not many patients are willing to accept life-long supportive therapy by stockings, but these have their place in the management of some individuals.

Treatment.

The treatment possible is of three main types: (i) stripping of veins; (ii) division and ligation ("cutting and tying"); (iii) injections.

Stripping.

Eradication of the condition by stripping of the veins is combined with a radical dissection of the respective terminations of the long or short saphenous veins, and on most occasions should be supplemented by the division and ligation of communicating veins, combined with the excision of other gross varicosities.

The limitations of stripping are as follows: (i) Veins other than long or short saphenous veins are usually affected. (ii) The operation misses the important ulcer-producing veins behind the line of the medial malleolus. (iii) It is often difficult to strip the entire affected vein. (iv) Tearing, "shredding" and incomplete intraluminar stripping occur, leaving behind segments which are sites of recurrences. (v) Stripping is likely to fail to produce a good long-term result unless combined with a proper groin dissection, and ligation and division of communicators as well as excision of other varicosities.

It is these things which are bringing even this most enlightened procedure into disrepute.

Sometimes a straight strip is impossible. Segmental stripping, aided by finger dissection through multiple incisions, must then be performed, and under no circumstances should technical difficulty in passing the stripper the entire length of the vein prevent complete eradication.

Division and Ligation.

Division and ligation is a satisfactory procedure only when applied to (i) local varicosities; (ii) incompetent communicators either in combination with stripping, or when stripping misses these veins—for example, behind the medial malleolus (the third saphenous system); (iii) local recurrences.

Cutting and tying combined with a groin dissection used to be the elective method of dealing with varicose veins; the results so obtained are grossly inferior to those of total eradication of the affected veins. It also makes revisionary procedures an almost impossible task.

Injections.

Injection treatment is included as part of operative treatment because it is usually complementary to surgical ablation. The indication for its use is the need to deal with remaining radicles and with small intracutaneous varicosities whose removal is desired for cosmetic reasons.

If injections are used with the aim of producing a cure of incompetent main venous channels, complete failure is guaranteed. Recanalization will always occur, and even if a local block has been produced, it is circumvented by the development of collaterals, which now become varicose (Figure IA and B).

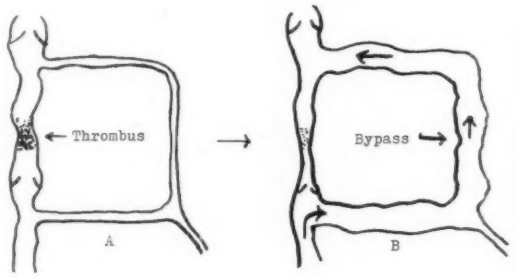

FIGURE I.

Injections should be by the "empty vein technique", whose aim is not to produce a thrombus but intimal damage leading to fibrous apposition of the wall. The technique is briefly described elsewhere (Stern, 1960).

It is apparent that surgical treatment consists of a combination of stripping, ligation of communicators and excision of veins, together with injection of radicles. These combined treatment methods cater for the varying conditions presented in the leg and allow maximum eradication. However, it must be made clear that no single operative procedure can eradicate each and every affected vein, and even were this is to be achieved it would be no guarantee that other and as yet normal veins would not become varicose. The acceptance of the concept that operation is but the beginning of a course of treatment which will need constant review and revision, is of fundamental importance.

What are our reasons for advising operation? We know that in the majority of patients the disease is progressive, and that it is almost never retrogressive. In those cases in which symptoms are due to varicose veins we can relieve these and get rid of distressing, diseased and unsightly deformities, having grossly faulty function and leading in some cases to even more distressing complications. Our advice must be tempered by consideration of the age, occupation and our general assessment of the patient, and our approach should not be rigid.

Indications for Operation.

Operation should be advised in patients with: (i) sapheno-femoral and/or sapheno-popliteal incompetence; (ii) sapheno-communicating vein incompetence; (iii) destruction of functioning valves from previous phlebitis; (iv) incompetent saphenous veins in the presence of patent, but incompetent, deep veins (the saphenous veins are only an added embarrassment, and contribute nothing towards a good circulation); (v) œdema, eczema, induration, pigmentation and ulceration (operation is deferred till these conditions have been controlled); (vi) symptoms disproportionate to apparent venous disease (there is no definite relationship between the symptoms and the extent of the disease, and each case is judged on its merits—compression bandaging should relieve the symptoms, and if these recur when this is discontinued, then operation should be advised after all other possible causes of the symptoms have been carefully excluded); (vii) unsightly deformities—the patient's wish for correction for cosmetic reasons must be respected.

Contraindications to Operation.

Contraindications to operation are: (i) recent phlebitis; (ii) the presence of infection or ulceration (till these are controlled, except when Cockett's operation is indicated); (iii) the presence of a pelvic tumour (as a cause of secondary varicose veins); (iv) deep venous obstruction; (v) marked arterial insufficiency; (vi) intercurrent disease; (vii) senility; (viii) pregnancy.

Operation should be an elective procedure, and is for a benign condition. No unnecessary risks must be taken, and since these operations are lengthy it is often better to restrict one operative session to one limb, rather than risk the sequels of prolonged operation. There should be no mortality and little morbidity from these procedures.

If the indications exist, operation should be undertaken as soon as conditions permit. Ulceration and infection should have been controlled for at least six weeks. Operation during pregnancy is hardly ever justified. While the veins undoubtedly become more prominent, regression after parturition is often remarkable and no decision regarding operation should be made for three months after confinement, when the residual condition is assessed. During pregnancy the legs require constant firm and adequate support, usually by stockings. However, Dodd (Dodd and Payling Wright, 1959), operates on pregnant women whose varicose veins are not controlled by other measures, and he reports good results.

The question of the timing of these operations to child-bearing often crops up. Whereas pregnancy undoubtedly accentuates the existing condition, this cannot occur if there are no diseased veins to accentuate. Operation should not be deferred on account of further pregnancies. Women having undergone operation usually have as little trouble with their legs as those who never have had any varicose veins.

The results of operation are, on the whole, very good if this has been properly adjudged and executed, and the patient has been regularly followed up. Satisfactory and lasting results can be obtained in 80% to 90% of cases, although revisionary procedures may become necessary from time to time.

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Reports of Cases.

ACUTE ASEPTIC MYOCARDITIS OF NEW-BORN INFANTS, DUE TO COXSACKIE VIRUSES.

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Myocarditis has been reported as occurring in association with several infectious diseases. This subject has been reviewed by several authors, the most recent being Manion (1956), who lists miscellaneous viral, bacterial, fungal and protozoal diseases as being in occasional instances associated with myocarditis. Myocarditis may also occur as an acute primary disease in the absence of any other sign of infection.

Until recently, in the majority of cases of non-suppurative, non-rheumatic myocarditis occurring in children, an ætiological agent has been lacking, although a viral cause has been postulated on the basis of the histological appearance of the myocardium. We present four fatal cases occurring sporadically in the neonatal period. In all a Coxsackie virus was isolated from the myocardium. The relation of these cases to epidemic Coxsackie virus disease of adults and older children is discussed.

Case I.

An infant girl, the fourth child of her parents, was born in October, 1956. The labour was normal, and the birth weight was 3360 grammes. The mother had suffered frequent "colds" during the pregnancy and had complained of abdominal pain during the two weeks before delivery. The baby seemed well until the age of six days, when she became pale and disinclined to feed, and her temperature rose to 39·5° C. Anorexia and fever continued, and two days later tachycardia, cyanosis, an enlarged liver and slight œdema were apparent. She was referred to the Royal Children's Hospital at this stage.

Examination of the patient on her admission showed her to be mildly distressed, with slight cyanosis. The temperature was normal (37·2° C). The heart sounds were rapid but regular, and no cardiac murmur was audible. The liver edge was palpable 4 cm. below the right costal margin, and there was slight pitting œdema of the legs. There was no jugular venous congestion. An X-ray examination of the chest showed cardiac enlargement, with early congestive changes in the lung fields. An electrocardiogram showed the features of supraventricular tachycardia, the rate being 240 per minute. Clinical examination of the ears, throat, lungs and central nervous system revealed no abnormality.

The infant was nursed in oxygen, and given tetracycline and digoxin. She died suddenly 14 hours after her admission to hospital, having shown no significant alteration in cardiac rate or rhythm since admission.

Autopsy.

A complete autopsy was performed. Specimens of tissue from selected organs were obtained for viral studies, and formalin-fixed sections from the major organs were stained with hæmatoxylin and eosin and examined microscopically. The relevant findings only are described.

The heart weighed 27 grammes (normal 20 to 21 grammes) and was of normal contour. Scattered petechial hæmorrhages were visible in the subpericardial layer, concentrated maximally in the region of the atrio-ventricular groove on the left. The myocardium was firm, but numerous petechial hæmorrhages were seen scattered through it. Confluent small hæmorrhages were present in the subendocardial layer overlying the central area of the upper half of the septal wall of the left ventricle, but were not visible elsewhere in the heart chambers. The foramen ovale and ductus arteriosus were functionally closed. The endocardium, valves, coronary arteries and great vessels were all macroscopically normal.

Both lungs were the site of diffusely scattered small hæmorrhagic lesions, and a few small areas of hæmorrhage were found in the subserosa of the bowel and in the thymus.

The liver was congested and weighed 127 grammes (normal 140 grammes).

Macroscopic examination of the remaining viscera revealed no abnormality.

Microscopic Findings.

The Heart.—Widespread myocardial damage was present. Many focal areas of necrosis of myocardial fibres were visible. In a number of these regions muscle fibres had disappeared, being replaced by a moderately dense accumulation of inflammatory cells amongst a few small fragments of eosinophilic debris. In other areas necrosis appeared to have been more recent, since the myocardial fibres could still be delineated, although their nuclei were pyknotic or fragmented, and the inflammatory cell infiltration was relatively sparse. The inflammatory cells were predominantly polymorphonuclear in type, but macrophages and small round cells were also present in considerable numbers. Less obvious degenerative change of varying degree was visible elsewhere through the major portion of the myocardium, and there was a slight infiltration of interstitial tissues generally, by inflammatory cells of the above-mentioned types. The subpericardial region appeared moderately œdematous, with congested blood vessels and

lymphatics, and contained moderate numbers of inflammatory cells. The endocardium appeared normal.

Other Organs.—Apart from the presence of areas of hæmorrhage in organs where this had been macroscopically apparent, and generalized congestive changes, no other abnormalities were found in sections of other organs.

Case II.

An infant girl was born prematurely in January, 1958, after an uneventful pregnancy and normal labour. Her weight at birth was 1930 grammes. The baby progressed well until the age of about three weeks, when failure to maintain her previously good weight gain became apparent. No other abnormality was noted until the age of 30 days, when she became listless and uninterested in feeding. An episode of cyanosis occurred that evening. She was examined by a local physician, who suspected the presence of pulmonary infection and administered penicillin. Death occurred suddenly next day at the age of 31 days. Autopsy was performed at the Royal Children's Hospital at the request of the local physician.

Autopsy.

The heart weighed 25 grammes (normal 14 to 15 grammes). The cardiac outline was slightly enlarged. The pericardial sac contained a slightly increased amount of fluid and a few flakes of fibrin. The myocardium was pale and mottled. The left ventricle was slightly dilated, but the other chambers appeared normal. The ductus arteriosus was closed, and the foramen ovale was functionally closed.

Both pleural cavities contained a considerable quantity of serous fluid. The underlying lungs were partly collapsed by the presence of the fluid, but showed no macroscopic evidence of consolidation.

The liver was congested and weighed 127 grammes (normal 90 grammes).

Microscopic Findings.

The Heart.—Focal areas of necrosis of muscle fibres associated with infiltration of leucocytes were present throughout the section. The left ventricular muscle appeared more extensively involved than the right.

The Pancreas.—One prominent and several small areas of necrosis, with associated collections of inflammatory cells, were present.

The Adrenal.—An occasional small necrotic focus associated with an inflammatory cell response was apparent.

Other Organs.—Apart from congestive changes, no significant abnormalities were found in the sections of other organs.

Case III.

An infant boy, the first child of his parents, was born in April, 1958, after an uneventful pregnancy and a normal labour. His condition at birth was good and his birth weight was 3500 grammes. At the age of 48 hours he developed jaundice, which temporarily deepened, but spontaneously subsided over the next four days. At this time investigations gave the following findings. The hæmoglobin value was 20 grammes per 100 ml. and the blood group was O, Rh-positive; the mother's blood group was B, Rh-positive. The jaundice was considered to be "physiological". The baby was otherwise well until the age of seven days, when he developed lethargy, pallor, cyanosis and a rapid, irregular pulse. He was referred to the Royal Children's Hospital.

Examination of the patient on his admission to hospital showed him to be in little apparent distress, but slightly cyanosed; this was relieved by nursing him in oxygen. The temperature was normal (36·9° C.), and the respiratory rate was 50 per minute. The heart sounds were rapid and irregular, but no cardiac murmur was audible. The liver edge was palpable 4 cm. below the right costal margin. There was no œdema or jugular venous congestion. An X-ray examination of the chest showed an enlarged heart with moderate congestive changes in the lung fields. An electrocardiogram showed dissociation of atrial and ventricular complexes, with an irregular ventricular rate of approximately 230 per minute. Clinical examination of the ears, throat, lungs and central nervous system revealed no abnormality.

The infant was given oxygen and digitalis. Seventeen hours after his admission to hospital, the cardiac rate and rhythm were virtually unaltered; but œdema of the eyelids and crepitations audible over the lung fields had developed. Cyanosis was now apparent, even in oxygen. Persistent irregular tachycardia, increasing cyanosis and the development of irregular breathing were features of the progressive deterioration, which terminated with death 26 hours after his admission, at the age of eight days.

Autopsy.

The heart weighed 26 grammes (normal 21 to 22 grammes), but had a normal contour. The pericardium was normal. The myocardium was congested and felt softer than usual. The endocardium was normal. The ductus arteriosus was patent, with an internal diameter of 3 mm. The foramen ovale was functionally closed. The great vessels and coronary arteries were normal. The liver was congested and weighed 145 grammes (normal 150 grammes).

Apart from congestion of some organs, no other abnormalities were found on macroscopic examination.

Microscopic Findings.

The Heart.—Widely distributed focal areas of myocardial degeneration and necrosis, associated with inflammatory cell aggregates, were present (Figure I).[1] The inflammatory cells were mainly large and small mononuclears, but a few polymorphs were present.

The Brain.—The meningeal and cerebral vessels were dilated, and a moderate number of inflammatory cells was present in the subarachnoid space. Small focal areas of necrosis and neuronal damage with associated inflammatory cell aggregates were visible in sections of the brain-stem (Figure II).

Other Organs.—Apart from congestive changes compatible with cardiac failure, no significant changes were seen in sections of other organs.

Case IV.

An infant girl, the fourth child of her parents, was delivered by forceps in September, 1958, because of delay in the second stage of labour. Her condition at birth was good, and her birth weight was 3080 grammes. The mother had been well during pregnancy until the day before labour began, when she developed fever (temperature 37·5° C.) and generalized pains, most marked in the region of the parotid salivary glands, although no parotid swelling was detected. It was stated by her general practitioner that there had been a mumps epidemic in the country town from which she came. Her symptoms and fever subsided within 24 hours. The baby appeared well until the age of seven days, when she was disinclined to feed. Next day her colour became grey, and tachycardia (at a rate of 160 per minute) was discovered. At the age of nine days her respiratory rate, previously normal, had risen to 50 per minute, and her other signs and symptoms were persisting. She was referred to the Royal Children's Hospital at this stage.

Examination of the baby on her admission showed her to be in little apparent distress, and with a "good colour". The temperature was 36·6° C. and the respiratory rate 60 per minute. The heart sounds were rapid but regular, and no cardiac murmur was audible. The liver edge was palpable 5 cm. below the right costal margin, and the spleen was just palpable. X-ray examination of the chest showed an enlarged heart and emphysematous lung fields. An electrocardiogram showed tachycardia (175 per minute)

[1] For Figures I, II and III see art-paper supplement.

with flat *T* waves and low-voltage complexes in all leads. Clinical examination of the ears, throat, lungs and central nervous system revealed no abnormality. Examination of the cerebro-spinal fluid (which was traumatically blood-stained) showed 5000 red blood cells, 4 polymorphs and 42 lymphocytes per cubic millimetre, and a protein content of 50 mg. per 100 ml.

The infant was given oxygen. Twelve hours after her admission to hospital, the pulse rate was 175 per minute and she was considerably paler than previously. Digitalization was commenced, but the baby died suddenly six hours later, at the age of 10 days.

TABLE I.
Summary of the Clinical Histories.

Case Number.	Sex.	Patient's Age at Onset.	Pathological Findings.	Age at Death.	Maternal Health.
I	F.	6 days	Myocarditis.	9 days	Ill two weeks before confinement.
II	F.	21 days	Myocarditis, meningo encephalitis, hepatitis.	30 days	Normal; baby premature.
III	M.	7 days	Myocarditis, meningoencephalitis.	8 days	Normal.
IV	F.	7 days	Myocarditis, inflammatory foci in adrenal and pancreas, necrosis of splenic follicles.	11 days	Aches, pains, fever 24 hours before confinement.

Autopsy.

The heart weighed 30 grammes (normal 20 to 21 grammes), but had normal contour. The myocardium had a normal macroscopic appearance, but felt soft and flabby. The endocardium and valves were normal. The foramen ovale was functionally closed. The ductus arteriosus was patent, just admitting a probe. The other great vessels and the coronary arteries were normal.

Apart from congestive changes, no abnormalities were seen in other organs.

Microscopic Findings.

The Heart.—Widespread focal areas of myocardial degenerative changes and necrosis were apparent. Aggregates of inflammatory cells, principally large and small mononuclear cells with occasional polymorphs, were present in the damaged regions.

The Spleen.—The Malpighian corpuscles were generally prominent. Many of them contained a necrotic centre occupied by finely granular basophilic and eosinophilic debris, with appearance suggestive of nuclear and cytoplasmic remnants respectively (Figure III).

The Brain.—The meninges were sparsely infiltrated with inflammatory cells, principally small round cells. A small perivascular inflammatory lesion was present in the white matter of the cerebellum.

The Liver.—A few small necrotic foci with associated inflammatory cell aggregates were seen.

Other Organs.—Apart from generalized congestive changes, no significant abnormalities were found in sections of other organs.

Laboratory Investigations.

Virus isolations were attempted from specimens taken as soon after death as possible. Organ suspensions were made by grinding the material with a sterile pestle in a sterile mortar with sand, after which 10 volumes of sterile Hank's solution containing penicillin and streptomycin were added. The suspensions were clarified by light centrifugation for 10 minutes. The specimens taken for study included heart, brain, blood and fæces.

The suspensions were inoculated to both of the following hosts, or to whichever one happened to be available on the day of receipt of the specimens: (*a*) suckling mice aged less than 24 hours (usually a litter of seven); (*b*) monkey kidney cells (rhesus) in monolayer culture.[1] The mice were inoculated by the intraperitoneal route with 0·05 ml., and the monkey cell cultures were inoculated with 0·1 ml. in batches of four.

The presence of a virus was detected as follows: (*a*) In suckling mice there appeared slight hind-leg paresis, unsteadiness of gait and incoordination at three to five days, followed over the next two or three days by severe paralysis and death. Histological examination of tissues from these mice indicated patchy myositis, meningo-encephalitis and fat-pad necrosis. Suspensions made from eviscerated, skinned carcasses readily produced a similar disease in further litters of suckling mice, but not in older mice. (*b*) In the monkey kidney cell monolayers, a rounding of the epithelial cells began at three days and had progressed to involve all cells by five days. The cytopathogenic effect (C.P.E.) of the isolate was insufficiently distinctive to suggest any particular virus.

Identification of virus isolates was made for preference in the monkey kidney cell cultures. However, in Case I the virus was identified provisionally in mice as a Coxsackie B virus on the basis of the histological appearance of skeletal muscle, brain and fat. A shortage of mouse families and of typing sera at that stage resulted in the specimen being submitted to Dr. Sidney Kibrick, of the Children's Medical Center, Boston, Massachusetts, U.S.A., who identified it as a Coxsackie virus, B2. The viruses isolated from Cases II, III and IV were typed locally, with the use of antisera prepared here against recognized types of the Coxsackie viruses. All three were Coxsackie B4.

Neutralization titres of the patients' and contacts' sera were determined in a similar manner to the typing test; that is, dilutions of heat-inactivated sera (56° C. for 30 min.) were made in the range of 1/20 to 1/640 in twofold steps. Viruses from Cases I and II were used as prototypes for these tests, and each was used at a concentration of 100 TCD_{50} per 0·1 ml. Equal volumes of virus and serum dilutions were incubated for 60 min. at 20° C., then 0·2 ml. was inoculated to each of 4 MK tubes. The cell cultures were examined for the absence of viral C.P.E. at the sixth day, and serum titres were expressed as that dilution preventing a 50% C.P.E.

Table II shows the details of the tissues examined, the viruses isolated and the serum neutralization titres obtained for these four patients and their contacts.

Discussion.

The Coxsackie subgroup of the enteroviruses has been recognized for 12 years now, each year resulting in the accumulation of further evidence of their rôle in human disease. Currently there is a total of 30 antigenically distinct types falling into two groups, A and B.

Basically, the two groups are differentiated experimentally by the clinical appearance and the pathological findings seen in suckling mice. In particular, the six group B viruses produce patchy myositis of skeletal muscle, meningoencephalitis and fat-pad necrosis, and occasionally myocarditis. In older mice under the influence of cortisone, the group B viruses may produce myocarditis (Kilbourne, 1956). All viruses of this group usually grow readily in monkey kidney cell monolayer cultures.

Clinically, the two groups of Coxsackie viruses are now accepted as the cause of some human diseases. Their occasional occurrence in association with other viruses, notably poliomyelitis virus, has tended to confuse the understanding of their role in some other diseases. However, it is well established that herpangina is caused by some of the group A viruses, and Bornholm disease (epidemic pleurodynia) by all the group B viruses. Members of both groups also cause aseptic meningitis, group B being better implicated.

The first two reports of the role of Coxsackie viruses in human myocarditis came from South African workers (Javet *et alii*, 1956; Montgomery *et alii*, 1955). Both series were associated with nursery outbreaks. Later reports from South Africa were also associated with nursery infection (Kipps, 1958). All other reported cases appeared to be sporadic in themselves, although occurring at times of epidemic disease of the general population.

It appears to us that the general picture of the disease as evidenced from the published reports is as follows.

[1] Obtained by courtesy of Dr. P. L. Bazeley, Commonwealth Serum Laboratories, Melbourne.

Neonatal Coxsackie group B virus myocarditis is a disease with a high mortality, occurring during periods of epidemic pleurodynia of the adult population. Infection may occur in utero and also by maternal or hospital cross-infection. In addition to the usual clinical and pathological signs of acute aseptic myocarditis, there is occasional evidence of the involvement of other organs.

TABLE II.

Summary of Virus Studies of Patients and Parents.[1]

Case Number and Date.	Findings in Specimens Studied.[2]	Virus Type.	Serum Specimens.	Neutralization Titres.[3] Cox-sackie B_1.	Cox-sackie B_2.	Cox-sackie B_4.
I: October, 1956.	Heart + Blood + Fæces −	Coxsackie B_2.	Mother 20/11 Mother 18/12		40 320	
II: January, 1958.	Heart + Brain + Blood + Fæces +	Coxsackie B_4.	Baby 17/1	−	−	−
III: April, 1958.	Heart + Blood + Fæces +	Coxsackie B_4.	Baby 22/4	−	>20	−
IV: September, 1958.	Heart + Brain + Blood − Fæces −	Coxsackie B_4.	Baby 9/8 Mother 17/9	− −	− −	− 80

[1] *Comments.* (*a*) Note the frequency of virus isolation: heart 4/4; blood 3/4; brain 2/2; fæces 2/4. Thus, had fæcal specimens only been studied, two cases would have been missed. (*b*) Coxsackie B_1 was included in the serology tests only because it was also epidemic during 1958. The Coxsackie B_2 antibody in the serum of Case III is probably maternal antibody. It may indicate maternal infection in a 1956 epidemic (Court and Jack, unpublished). (*c*) The rising titre in the paired sera of the mother in Case I indicates that she was infected with the same virus. A relatively low titre of 40 in serum taken one month after the child's death suggests that the mother's infection may have occurred some days later. (*d*) In the three tests of babies' sera, it appears that none had maternal antibody to Coxsackie B_2, the causative agent of their infection. (*e*) The titre of 80 in the serum of the mother in Case IV, taken six weeks after her pre-confinement illness, may suggest that this also was a Coxsackie B_4 infection. Studies with mumps complement-fixing antigen (soluble) indicate that her parotid soreness was not due to mumps virus infection.

[2] Positive isolation: +.

[3] Reciprocal of endpoint dilution: " − " refers to titres of less than 20.

The four cases described in this report measure up to this over-all picture in most respects. All progressed rapidly to a fatal termination. All four children were aged less than four weeks. None appeared to have been infected in utero, if an incubation period of two to three days is assumed (Kibrick and Benirschke, 1958). All cases occurred during periods of Coxsackie virus infection of the general population of Melbourne (Jack, unpublished). In Case IV it seems on the clinical and serological evidence not unlikely that the baby was infected by the mother *post partum*. In Case I, infection of the mother was probably subsequent to that of the baby, and possibly both were exposed to the same source of hospital infection. In Cases II and III, there was no evidence to suggest the route by which infection occurred. No patient had clinical signs referable to the involvement of any organs other than the heart, but with the exception of Case I, there was histological evidence of lesions in other organs (Table I).

In the published reports there are two points of divergence from the general picture outlined above. Although the majority of infections has occurred in new-born children, Hosier and Newton (1958) report one fatal case in a child aged seven weeks, and one non-fatal case in a child aged five years, in whom fæcal excretion of virus was associated with a fivefold rise in homologous neutralizing antibody during convalescence. Hosier and Newton also differ with regard to the usual finding of epidemic disease due to the same virus being present in the community at the same time, so stressing that a Coxsackie virus ætiology of neonatal myocarditis should not be ignored in non-epidemic periods.

It is possible that the rôle of Coxsackie viruses in acute aseptic myocarditis may be centred in new-born infants, and that the myocarditis of older children, if viral in origin, may be due to other viruses. However, the knowledge that Coxsackie group B viruses are one cause makes possible a serological evaluation of those older children who recover and from whom no virus is isolated. A maximum of six neutralization tests would remove suspicion from the Coxsackie group B viruses. Further, in a case of sudden death of either a new-born or an older infant (in addition to histological and virus studies at autopsy), it will be worth while to study the family contacts for evidence of recent infection with these Coxsackie viruses.

The variety in nomenclature used to describe cases of acute myocarditis is confusing, and in part this is due to uncertainty of ætiology. Saphir and Cohen (1957) still consider there is reason for retaining the term "isolated myocarditis", by which they mean "of unknown cause . . . occurring in the absence of any disease known to cause myocarditis". They also stress that in the proved viral forms of myocarditis there are necrotic foci of inflammation, and that in the other cases, of suspected but unproved viral ætiology, extensive interstitial involvement without necrosis is present.

Kibrick and Benirschke (1956) have used the term "acute aseptic myocarditis" in analogy with that term now used for viral meningitis. We are in agreement with this terminology, for, as in the case of the meningitides whose diverse viral ætiology has been appreciated in recent years only, the term could be qualified by the type of virus as recognized.

Summary.

The clinical and pathological findings are described for four cases of acute aseptic myocarditis in the neonatal period.

A Coxsackie group B virus was isolated from the myocardium in each.

Associated epidemiological findings are also discussed.

Acknowledgements.

We are indebted to Dr. A. L. Williams, Dr. A. W. Venables and Dr. J. W. Perry for advice and criticism during this investigation. Dr. Williams and Dr. R. A. Chenoweth performed the autopsies in Cases I and II respectively. Mrs. Joan Dwyer gave valuable technical assistance. Our thanks are also due to members of the senior medical staff of the Royal Children's Hospital for permission to quote from their case records.

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Legends to Illustrations.

FIGURE I.—Section of myocardium (Case III), showing areas of muscle destruction accompanied by inflammatory reaction. (Hæmatoxylin and eosin stain, × 53.)

FIGURE II.—Section of portion of medulla (Case III), showing a small area of encephalitis. (Hæmatoxylin and eosin stain, × 150.)

FIGURE III.—Section of spleen (Case IV), showing an area of necrosis within a germinal centre. (Hæmatoxylin and eosin stain, × 150.)

NEONATAL COLD INJURY.

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THERE is a critical range of environmental temperature within which the new-born infant can maintain his body temperature with the least possible expenditure of energy, and, as a consequence, his maximum resources will be available for survival or growth (McCance, 1959). As the temperature to which the infant is exposed falls, a level is reached at which the heat-regulating mechanism is unable to maintain body temperature and hypothermia develops.

There is no evidence that a subnormal temperature is ever in itself beneficial to a young infant (McCance, 1959), and although some infants tolerate such a state well, others develop the clinical picture for which Mann and Elliott (1957) have recommended the name "neonatal cold injury".

Five babies with hypothermia were admitted to the children's ward of the Mater Hospital, Newcastle, within a period of three weeks during the winter of 1960; one such patient had been admitted in the preceding winter. The cases are presented to emphasize that the dangerous condition, neonatal cold injury, can occur in regions generally not considered to have a cold climate.

Case I.

After 38 weeks' gestation, a male infant, A., was delivered by Cæsarean section because of increasing maternal toxæmia, an unfavourable cervix and unstable intrauterine fixation. His birth weight was 5 lb., and his condition in the immediate neonatal period gave no cause for concern. He was discharged from the Mater Hospital on the seventh day of life, feeding vigorously and in good health. On August 6, 1960, at the age of 12 days, he was readmitted to hospital after 48 hours of increasing lethargy and persistent refusal to suck. His intake of milk in that 48-hour period was estimated at only 4 oz., and information was advanced that he had passed urine only once in that time. Some 24 hours prior to his admission to hospital, the parents noticed that the baby felt cold to the touch, and wrapped him tightly in thick blankets. A. came from a good home, had much attention lavished upon him and had been nursed in his parents' bedroom, which was not heated. The minimum temperatures recorded in Newcastle in the four days preceding his admission to hospital were 45·2° F., 43·1° F., 40·9° F. and 46·9° F., and the maximum temperature in this period was 65° F.

On examination, the patient was inactive and strikingly cold to the touch, and gave a minimal response to external stimuli. Respiratory excursions were shallow and infrequent, and the pulse rate was 80 per minute. There was widespread erythema of the skin, especially pronounced on the face and overlying the distal portions of the extremities. Pitting œdema was present on the dorsum of the hands and feet and over the lateral surface of the distal third of the legs. The rectal temperature was 79° F.

Gradual rewarming was carried out in an incubator maintained at 80° F., and the patient was left undisturbed with no immediate attempt at feeding. Over the next 72 hours, as the rectal temperature rose to near-normal levels he became correspondingly more active, and by the fourth day he was taking his feedings satisfactorily so was taken out of the incubator. Chloramphenicol had been given subcutaneously throughout this period. A. was discharged from hospital six days after his admission, and subsequently has thrived.

Case II.

B., weighing 5 lb. 6 oz., was the first born of binovular twins, whose gestation period was estimated to be 42 weeks. His mother had a mild degree of toxæmia. The baby's condition was satisfactory in the immediate neonatal period, and he was discharged from the nursery of the Mater Hospital at the age of 14 days, in good health. Four days later he was noticed to be listless and difficult to rouse, and he refused to suck. Symptoms persisted, and on August 7, at the age of 20 days, he was admitted to the children's ward. His twin sister had remained well throughout this period. The minimum temperatures in Newcastle in the four days preceding his admission were 43·1° F., 40·9° F., 46·9° F. and 45·5° F., and the maximum temperature was 65° F. No history of direct exposure to cold was obtained.

At the time of his admission B. was inactive and cold to the touch; œdema was present over the distal portions of the limbs, and there was pronounced erythema of the cheeks, the tip of the nose and the distal parts of the extremities. The rectal temperature was 85° F.

He was placed in an incubator maintained at 85° F., and over the next 36 hours his temperature rose slowly and activity increased. After 48 hours he was having his usual feedings and was taken out of the incubator. Frequent mucous stools were passed in the 24-hour period following his admission to hospital, but subsequently the stools returned to a normal consistency. Chloramphenicol was given by the subcutaneous route during the first four days of treatment. Five days after his admission he was discharged from hospital and he has since progressed satisfactorily.

Case III.

C., whose birth weight was 4 lb. 12 oz., was born at the Mater Hospital after a gestation period estimated at 38 weeks. Pregnancy and labour were not complicated, and the baby was discharged from hospital at the age of 8 days after an uneventful immediate neonatal period. He was readmitted to hospital on August 9, 1960, at the age of 12 days, with a 24 hours' history of lethargy, difficulty in being roused and refusal to suck. The minimum temperatures in Newcastle on the days preceding his readmission were 46·9° F., 45·5° F., 42·9° F. and 39·8° F., and the maximum temperature was 64° F.

On examination C. was very cold to the touch. Pitting œdema was present on the dorsa of the feet and the lateral portion of the distal third of the legs with erythema, which was particularly prominent in the extremities, over the cheeks and on the tip of the nose. Response to external stimuli was poor, the pulse was slow and respirations were shallow and infrequent. The rectal temperature was 74° F.

Warming in the incubator resulted in a gradual small increase in rectal temperature, but no concomitant improvement in the baby's general condition. Glucose solution given orally was vomited, so on his second day in hospital a small quantity was given intravenously. However, soon after this administration was commenced respiration became further depressed, moist râles appeared throughout both lung fields and the infant died.

At autopsy, sterile pulmonary hæmorrhage in both lungs was the only abnormality found. Microscopic study revealed a fairly gross degree of pulmonary intra-alveolar hæmorrhage. A small number of alveoli were filled with polymorphs. No clumps of bacteria were seen.

Case IV.

D. was born after an estimated gestation period of 35 weeks, and weighed 5 lb. 3 oz. His mother had mild toxæmia of pregnancy. Labour and the immediate neonatal period were unremarkable, and the baby was discharged on the seventh day of life in apparent good health. Three days after his discharge from hospital he was observed to be cold to the touch, and was wrapped in cotton-wool. He later became increasingly lethargic and difficult to rouse, and he refused to suck. He was readmitted to the Mater Hospital on August 15, 1960, at the age of 12 days. The minimum temperatures in Newcastle on the days preceding the readmission were 40·1° F., 44·5° F., 46·0° F. and 46·8° F., and the maximum temperature was 68° F.

On examination of the baby, there was extreme inactivity, with facial erythema and pitting œdema of the feet and the lowermost portions of the legs. The rectal temperature was 80° F.

With rewarming in the incubator there was a gradual rise of temperature, the infant became progressively more active, and after 48 hours, when his temperature had reached 92° F., D was taking orally small amounts of glucose. However some 72 hours after his admission to hospital there was a sudden deterioration in his condition. He became cyanosed respiratory excursions were shallow and rapid, signs of circulatory failure appeared and he died four hours after the onset of this acute episode.

At autopsy extensive pulmonary hæmorrhage was observed, together with fresh blood in the cranial cavity suggesting a recent cerebral hæmorrhage. Microscopic examination of the lung lesion revealed small areas of atelectasis, a mild degree of capillary congestion and occasional alveoli filled with polymorphonuclear leucocytes. No bacteria were visible.

Case V.

E. was born in another hospital where no form of external heating is used in the nursery. Her mother had severe toxæmia, labour was uneventful and the birth weight was 5 lb. The immediate neonatal period was complicated by difficulty with feeding, repeated vomiting and abdominal distension. There was a steady deterioration in her condition, and fluid was given by subcutaneous infusion in the thigh. She was transferred to the children's ward of the Mater Hospital on July 24, 1960, at the age of five days. The minimum temperatures in Newcastle in these five days ranged from 38·6° F. to 50·9° F., and the maximum temperatures from 58° F. to 68° F.

On examination of the baby, there was extreme immobility with minimal response to external stimuli, facial erythema, pitting œdema over the feet and distal portion of the legs (more marked in the leg used for the subcutaneous infusion) and tympanitic distension of the abdomen. The rectal temperature, which previously had not recorded on a thermometer with a minimum reading of 85° F., reached 88° F. after the transfer in a warmed incubator.

At the Mater Hospital she was placed in a "Humidicrib" maintained at 90° F. Although there was a rise to 94° F. in her rectal temperature, there was no significant improvement in general condition, and she died 15 hours after her admission.

At autopsy, extensive pulmonary hæmorrhage was found, with dilatation of the large bowel extending from the middle of the descending colon to the anus. Ganglia were present in what was considered normal numbers in the sections taken from the affected areas. Microscopic examination of sections of the lung revealed gross pulmonary intraalveolar hæmorrhage. Some alveoli, particularly around the bronchioles, were filled by polymorphs. No bacteria were seen.

Case VI.

F. was born on July 24, 1959, in a small private maternity hospital in Newcastle. Her primiparous mother had toxæmia, necessitating admission to hospital some two weeks before the expected date of confinement. Labour was within normal limits, the baby's birth weight was 6 lb. 4 oz., and her condition after delivery was satisfactory. She was first examined by one of us (R.B.M.) on the third day of life, because she had developed pitting œdema of the feet and lateral surface of the distal portions of the legs, as had four of the other 11 infants in the nursery at that time. F. was the most severely affected, the dorsa of her hands also being involved, and her cheeks were strikingly red in colour. She was lethargic and refused to suck, and on palpation it was obvious that she was grossly hypothermic. Her rectal temperature was 74° F., and that of the other affected babies ranged from 82° F. to 90° F. The temperature in the unwarmed nursery at 10 a.m. was 58° F., but doubtless had been lower during the preceding night, in which the minimum temperature in Newcastle was 42·9° F.

When the nursery was heated by radiators and maintained at 70° F., symptoms and signs in the other four affected infants resolved over the following three days. F.'s temperature rose slowly, but her condition remained poor, and feeding effort was unsatisfactory. On the fifth day of life œdema of the abdominal wall developed, and was followed a day later by abdominal distension and the passage of frequent mucous stools.

When her condition deteriorated further, she was transferred to the children's ward of the Mater Hospital at the age of nine days. Abdominal distension increased, she vomited frequently, the mucous stools became flecked with blood, and in the perianal area weeping excoriation developed. The stools remained sterile. "Chloromycetin" therapy was started to counteract any sepsis.

Death occurred on the thirteenth day of life, and autopsy revealed colitis with extensive mucosal ulceration and adjacent patches of fibrinous peritonitis. *Proteus vulgaris* was cultured from the involved areas found at autopsy.

Discussion.

Lethargy, immobility, refusal to suck, redness of the skin (particularly of the face), coldness to the touch and a temperature below 90° F. are the symptoms and signs of neonatal cold injury. As Mann and Elliott (1957) have stressed, the patient with his rosy cheeks and "serene air" may look healthy even when gravely ill. However, the striking coldness of his body leaves little doubt of the presence of abnormality. In these six patients rectal temperatures ranged from 74° to 85° F., but owing to peripheral vasoconstriction the skin temperatures would have been considerably below these levels and probably approached that of the environment. This characteristic, intensely cold outer layer acts to a certain extent as an insulator, protecting the "core" against further cooling.

The major ætiological factor in neonatal cold injury is considered to be the low environmental temperature. This small series would appear to support this premise, as in the four infants born in the Mater Hospital, where the nursery is warmed to a temperature of 70° F., symptoms and signs developed only after their discharge from hospital and, presumably, exposure to cold. The other two infants developed the condition whilst in unheated nurseries. In the majority of the cases reported by Bower *et alii* (1960), symptoms developed within the first three days of life. His series, in the main, was made up of domiciliary deliveries, and exposure occurred at an earlier age than in the Mater Hospital group, in which the average age of onset was 12 days. These four last-mentioned patients were all admitted in a ten-day period, in which the district minimum daily temperatures ranged from 39·8° to 46·9° F., and the maximum temperatures from 57° to 68° F. Of the 70 cases reported by Bower *et alii* (1960), in 53 instances the causal minimum temperature was below 35° F., and in only nine cases was the minimum temperature greater than 40° F.

Apart from the low external environmental temperature, other factors could predispose the infant towards neonatal cold injury. Five of the six babies in this report weighed between 4 lb. 12 oz. and 5 lb. 6 oz., and the average weight of the group was only 5 lb. 4 oz. It is possible that infants about 5 lb. in weight may be particularly susceptible to this condition. Not only does a lack of insulating subcutaneous fat and a large comparative surface area make heat conservation difficult, but also their birth weight just precludes them from the protective care accorded to "premature" babies, notwithstanding that the efficiency of the heat-regulating mechanisms may be little different in the two groups.

Maternal toxæmia was present in five of the six cases. The frequency of this possible predisposing factor is not commented upon in the series of Mann and Elliott (1957) or of Bower *et alii* (1960). In the latter series, vomiting was a feature in 12 of the 70 cases of "primary" cold injury (in which external chilling is the major ætiological factor). In the cases reported here, it occurred in three infants, and in two of these abnormalities of the large bowel were present at autopsy. In Case V, ill health and vomiting were reported to have been present from birth. Although this may indicate that some factor other than exposure to cold also contributed to the infant's condition, it is interesting to note that 22 of the 70 patients of Bower *et alii* with "primary" cold injury were "unwell from birth"; this suggests that exposure in the period following delivery may be an important one in the ætiology of this condition. Chilling may occur if the infant is left uncovered during the third stage of labour or during his bath, if these procedures are carried out in cold rooms.

In Case VI, bowel symptoms developed after the onset of hypothermia, and although infection possibly played a part in this baby's eventual death, it is likely that exposure to cold was the primary cause of her illness. The ulceration of the colon found at autopsy in this patient may be related to the hæmorrhages found beneath the serosal surface of the colon in two of the eight autopsies performed in the series of Mann and Elliott (1957).

The cerebral hæmorrhage in Case IV is unlikely to have been related to birth injury, because of the period of apparent well-being preceding the onset of symptoms at the age of 15 days. Rather it would seem to be part of the hæmorrhagic process responsible for the pulmonary hæmorrhage found at autopsy in three of the four fatal cases reported here, in five of eight fatal cases of Mann and Elliott (1957) and in 11 of the 15 fatal cases of Bower *et alii* (1960). Recently Edwards and Gresham (1960) have reported extensive intraalveolar hæmorrhage as one of the three broad histological groups in staphylococcal pneumonia in the neonatal period. In their two cases in which hæmorrhagic lesions were present, there was associated necrosis of the alveolar walls, and abundant staphylococci were evident in the sections. Neither of these features was obvious in the lung sections reviewed here; but the findings in Case III, Case IV and particularly Case V suggest that early lung infection (probably not staphylococcal) was present at the time of death. Whether such infection follows exposure to cold, or whether it is an essential ætiological factor, together with exposure, in producing the clinical picture of neonatal cold injury, remains a matter of conjecture.

Death followed neonatal cold injury in eight of the 14 cases of Mann and Elliott, in 18 of the 70 cases of Bower *et alii* and in four of the present group of six cases. Prevention of this condition depends on protection from cold environmental temperatures. Mann and Elliott have suggested measures to avoid chilling of infants born at home during the English winter. In Australian "cold snaps" these are equally applicable, both in the hospital nursery and later in the home. The most elementary of these prophylactic measures is the maintenance of an environmental temperature greater than 65° F. for the first 14 days of life, and for even longer periods for premature and other small babies. This is preferable to wrapping the infant in several layers of clothing and blankets, as this tends to prevent limb movements and so intereferes with heat production. If the baby should become chilled, then, of course, these layers by their insulating action make rewarming more difficult. If suitable instructions were given to parents of babies born in the colder months at the time of discharge from warmed hospital nurseries, the lives of some Australian babies would be saved each year.

The treatment of established neonatal cold injury is not yet clearly defined. Slow rewarming generally is recommended, and Mann and Elliott (1957) and McCance (1959) also suggest that glucose be administered to counteract associated hypoglycæmia. The possibility that sepsis may be a predisposing factor, and the frequent absence of specific signs of infection in this group of patients, suggest that antibiotics would be indicated.

Summary.

Six patients with neonatal cold injury admitted to the children's ward of the Mater Hospital, Newcastle, are discussed. Four of the patients were admitted in a ten-day period during a "cold snap". The dangers of exposing new-born infants to a low environmental temperature are discussed.

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Reviews.

The Chemistry of Thyroid Disease. By Rosalind Pitt-Rivers, M.Sc., Ph.D. (London), F.R.S., and Jamshed R. Tata, M.Sc. (Bangalore), Docteur es Sciences (Paris); 1960. Springfield, Illinois: Charles C. Thomas, and Oxford: Blackwell Scientific Publications Ltd. 9" × 6", pp. 96, with figures. Price: 36s. (English).

THIS volume is one of a series designed to inform the practising physician of the more recent contributions of the basic chemical sciences to subjects of clinical interest. Both Dr. Pitt-Rivers and Dr. Tata have world-wide reputations for their research on thyroid diseases. They describe the biosynthesis, circulation and metabolism of the thyroid hormone in normal persons, and relate this knowledge to the pathophysiology of hyperthyroidism and hypothyroidism. There is a useful review of the recently described genetic causes of critinism. Hashimoto's disease is covered in a separate chapter, and the authors have included a short description of the experimental techniques used to study the immunological aspects of this condition. Readers will find little of practical value in the discussion of thyroid carcinoma.

The text of this monograph is very brief (68 pages), and simplicity of style has been maintained throughout. As can readily be understood, there has been no attempt to describe either the clinical manifestations of thyroid disease or the biochemical actions of thyroid hormone within the individual cell.

Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and its Allied Professions. By Arthur Grollman, Ph.D., M.D., F.A.C.P.; third edition; 1958. Philadelphia: Lea & Febiger. 9" × 5½", pp. 1336, with illustrations. Price: £6 17s. 6d.

THIS textbook which was originally Cushny's "Pharmacology", is now in its fourth edition, and this follows closely on the third a couple of years ago. This is quite a substantial book of 44 chapters covering the whole range of drugs used in medicine. Each chapter contains a detailed description of the drugs in question, their sources, chemistry, pharmacology and uses, and at the end is given a list of the preparations currently in use in the United States and

referred to in the U.S. Pharmacopœia and also those to be found in the British Pharmacopœia. Finally there is a useful list of the main references appropriate to the chapter. Although the book is therefore very detailed, it is nevertheless quite readable, and although it bears very little resemblance to the original editions of Arthur Cushny, the critical and scientific approach which he used is still maintained in it. The new edition contains some excellent illustrations, and is certainly thoroughly up to date. The production of the book is of the highest quality, a quality we have come to expect of the best American publications, so that it is a pleasure to handle for this reason alone. The book is neither a textbook of fundamental pharmacology nor one of clinical or applied pharmacology; it is, in fact, a happy combination of both. It is not a book we would recommend to students studying pharmacology for the first time, but it is a book which will be very valuable to the advanced medical student in his fifth or sixth year, and equally valuable to the practising medical man who needs to have at hand a reliable reference source.

Dilling's Clinical Pharmacology. Revised by Stanley Alstead, C.B.E., M.D., F.R.F.P.S. (Lond.), F.R.C.P. (Edin.), F.R.S. (Edin.); twentieth edition; 1960. London: Cassell & Company Ltd. 7¼" × 5", pp. 876. Price: 30s. net (English).

"DILLING" has been with us for a long time—in fact, the first edition was made in 1884—and is still one of the most popular student textbooks in clinical pharmacology. The new edition is certainly well overdue, since the last one in 1951 is by now completely out of date. The whole emphasis of this textbook is on the clinical side of pharmacology, and it is divided into some 23 chapters dealing with the action of drugs on different systems of the body. These chapters provide a complete coverage of the drugs used frequently in medicine today. At the beginning of each chapter a page or two is devoted to fundamental considerations of the biochemistry, pharmacology and chemistry of the systems discussed and the drugs which act thereon. After this, the principal drugs of the group are discussed in detail, and after them those less commonly used in somewhat lesser detail. At the end of the book there is a series of very useful appendices; the first of these deals with pharmaceutical terms which are still used in medicine to an appreciable extent; then follows a formulary, which is really a brief therapeutic index. The next appendix deals with a short course in practical pharmacology and pharmacy; this is really a course in *materia medica* and dispensing, and is perhaps one of the least significant features of the book. The fourth appendix is an explanation of the chemical nomenclature of drugs; this is interesting and useful, because often the medical student—and the medical man also, for that matter—find this very confusing. The format of this book is very convenient, because the type, although somewhat small, is easily readable, the margins have been restricted and the book will comfortably fit into a not-too-small pocket.

In summary, therefore, "Dilling" still represents a very good general textbook for the senior student. The practising physician may find the book rather elementary, and although a section of bibliography is given in an appendix, the detail which is involved in the chapters is often not as great as one would like. The section dealing with hypotensive drugs, for example, is rather thin, since no mention is made of the more recent drugs such as bretylium or guanethidine; and the mode of action attributed to rauwolfia is not that which we would consider to be responsible for its hypotensive effect at the present time. These criticisms are small ones, because generally the book is very well produced and free of errors, and undoubtedly will be read by many and find a very useful place in the textbooks of medicine.

Principles of Bone X-Ray Diagnosis. By George Simon, M.D., M.R.C.P., F.F.R.; 1960. London: Butterworth & Co. (Publishers) Ltd. 10¾" × 8¼", pp. 204, with many illustrations. Price: 78s. 6d.

ALL who have read Dr. George Simon's excellent book on diseases of the chest will expect a great deal of this recently published and comparable work. In this he adopts the same unusual approach used previously, insofar as diseases are grouped according to the type of X-ray picture they produce. While this approach is not the unqualified success it proved to be in the case of diseases of the chest, it certainly leads to a fascinating and original presentation of familiar problems, which is itself instructive. Many interesting and valuable facts in respect to the similarities and differences of various disease processes from a radiological viewpoint are set down clearly and concisely. The text is refreshingly free from cant, while the reliability of various X-ray signs is honestly discussed and the limitations of the method are indicated. As well as stressing distinctive and diagnostic signs in the conventional manner, the author goes to great pains to indicate those conditions under which it may be difficult or impossible to differentiate radiologically between two differing disease processes.

The author is at his best when he discusses certain specific problems, such as the causes of the collapse of a single vertebra or the differential diagnosis of a local translucent area in the vault of the skull, to quote but two examples. Discussion of numerous such finite problems is set down with skill and discernment, and from these the reader draws heavily on the rich experience of the author. This is not a textbook of bone diseases, and many important sections are only touched. The student radiologist must read his textbooks first, and will then find in Dr. Simon's book a series of invaluable tutorials and a stimulus to logical thought. The orthopædic surgeon will find much of value and interest here, and no one with an interest in radiology will read this book without profit.

The discussion of malignant neoplastic lesions, which fall for the most part under the heading of "Periosteal Opacity and Erosion", is to be commended, and giant-cell tumours and their variants are simply and sensibly dealt with. There is a useful section on rheumatoid arthritis and related diseases.

The text is supported by a large and beautifully selected series of radiographs, which are vital to a work of this nature.

A Textbook of Clinical Pathology. Edited by Seward E. Miller, M.D.; sixth edition; 1960. Baltimore: The Williams & Wilkins Company. 10" × 6½", pp. 916, with illustrations. Price: £8 5s.

THIS large book, now in its sixth edition, is edited and partly written by a physician for physicians and teachers of medicine, as well as for medical students, interns and clinical pathologists. According to the preface, "it portrays what tests to order, when in the course of disease to order them, how to interpret and evaluate the results; in short, the use of the clinical laboratory in differential diagnosis and in following the course of disease in patients. This approach is coupled with continued emphasis on normal function and the mechanism of disease". It comprises 26 chapters, written by 13 contributors, four of whom are professors of medicine or of internal medicine, the remainder being professors or workers of professorial status in one of the branches of clinical pathology. The first five chapters, dealing with hæmatology, are very well written and illustrated. Chapters on "The Diagnosis of Bacterial Infections", "The Assay of Chemotherapeutic and Antibiotic Agents", "The Diagnosis of Viral and Rickettsial Disease" and "Saliva, Sputum and Bronchial Exudates" are full of useful information presented in a fresh and stimulating way. The section on "Medical Parasitology" is good in parts, but curiously uneven; there are, for instance, no pictures of hydatid elements. Chapters on "Seminal Fluid" and on "Feces" are quite inadequate and lack illustrations. A compendium such as this suffers by comparison with standard textbooks on the various branches of clinical pathology. This subject has grown too big to be dealt with adequately in one volume. However, it is a most readable volume, excellently printed and produced, and may well be of great use to the busy physician or intern, who will find it a reliable guide to intelligent cooperation with his colleagues in the clinical laboratory.

Treatment of Emotional Problems in Office Practice. By Frank F. Tallman, M.D.; 1961. New York, Toronto, London: McGraw-Hill Book Company, Inc. 8" × 5¼", pp. 446. Price: $11.00.

THIS book is based on a series of lectures and seminars held under the auspices of the Medical Extension Division of the University of California. The first part, "Personality Growth and Function", deals with the characteristics and special stresses of the various age periods in the life of the individual. This is followed by a history of theories regarding mind-body relationships and a review of neurophysiology, with special reference to the mechanisms of offence and defence, in which the author points out that while drugs may control emotional reactions, psychotherapy is needed to help the patients to solve the conflicts which have stirred up the emotions. The term "psychosomatic" is regarded as a "semantic superfluity". In the chapter on

"Symptom Formation", Dr. Tallman has made extensive use of samples of communication between doctor and patient. In examination and diagnosis, emphasis is laid on "active listening, careful observation of non-verbal responses, pertinent questions and conscious effort not to supply the answers". The book does not deal with the handling of psychotic states, except that in Chapter 14, "Depressions and Suicide", indications for handing over the patient for specialist treatment are discussed in some detail. The treatment for psychoneurotic states which the physician should undertake in his surgery includes advice, guidance, suggestion, persuasion, reassurance, confrontation, insight therapy and interpretation. The doctor should beware of treating a psychoneurotic at home, lest he find himself the "victim of neurotic tyranny". Seminars on three cases reported in the appendix would have been more instructive had these cases been closed and summarized. This practical book, refreshingly free from psychiatric jargon and unverified theories, is full of sound advice based on experience.

Anæsthetic Accidents: The Complications of General and Regional Anæsthesia. By V. Keating, M.B., B.Ch., D.A., F.F.A.R.C.S.; second edition; 1961. London: Lloyd-Luke (Medical Books) Ltd. 8¾" × 5½", pp. 296. Price: 28s. net (English).

IN comparison with its precursor, the second edition of this book exhibits many improvements and evidence of much careful—indeed, painstaking—revision. The subject matter has been brought thoroughly up to date by the interpolation of additional comments, paragraphs and even new sections where required, and yet there has been no hesitation in discarding redundant or speculative material. Lucidity is thus improved, and controversial features are largely eliminated.

The book has been enlarged by 27 pages, to a total of 288. The first half deals exhaustively with the circulatory, cardiac and respiratory hazards of general anæsthesia, and includes a searching discussion of pulmonary complications. Later chapters on the barbiturates for intravenous use, the complications of local and spinal analgesia and of endotracheal anæsthesia, and the side-actions of the relaxants are all of excellent quality. Those on neurological complications and the adverse effects of various postures are somewhat restricted as to detail, although quite informative within their limitations. The sundry final chapters on infected apparatus, fires and explosions, miscellaneous accidents and medico-legal considerations are in general too brief to be of much value. The index, although now briefer and more systematic, could well be made to comprise much wider detail.

There are few errors, and very occasional examples of obscurity. Of the former "Ammophyllin" now appears on page 108, while later on "Megamide" and "Laudolyssin" are mentioned, despite the author's evident pains to exclude trade names elsewhere. In addition it would seem that 70% rather than 30% of nitrous oxide, as stated on page 265, would be the lowest concentration likely to maintain unconsciousness during operations requiring profound relaxation. Examples of obscurity are to be found in the discussion of the Hering-Breuer reflex on page 66; in that concerning vomiting on page 129, where one is advised to "roll a swab down the pharynx and insert a laryngoscope"; in the uninformative generalities about obstruction on page 141, which ignore the importance of chin-support and the lateral posture; in the remark about œdema of muscle on page 159; and in the mention of manual versus mechanical artificial ventilation on page 202. Nevertheless, this is an excellent book, and should be read by all doctors, especially anæsthetists and surgeons.

Aids to Theatre Technique: A Complete Textbook for the Nurse. By Marjorie Houghton, M.B.E., S.R.N., S.C.M.D.N., and Jean Hudd, S.R.N.; third edition; 1961. London: Baillière, Tindall & Cox. 6" × 4", pp. 234, with illustrations. Price: 8s. 6d. (English).

THIS book is one of the Nurses' Aid Series, and its popularity is shown in that it was first published in 1944 and that both the first and second editions were reprinted three times.

The book opens with an excellent discussion on the operating theatre unit, followed by a description of the modern theatre table and the different positions for which it may be used. A very full chapter on all aspects of sterilization follows. The duties of the theatre nurse are described in detail, and then follows a chapter on those of the anæsthetic nurse. The duties of the theatre staff in cardiac arrest are adequately described.

A useful glossary of technical terms used in operative surgery precedes the various chapters on the operations used in general and special surgery. Each chapter lists and illustrates the instruments required, and the needles and sutures commonly used, in various operations.

Traumatic surgery is dealt with fully, this section commencing with the organization of theatres in a casualty station dealing with large numbers of casualties including their resuscitation.

A chapter on the various methods of using radium in the theatre is very useful indeed.

A description of plaster of Paris technique concludes the book.

This book is indeed a good book, not only for nurses engaged in operating theatre work, but also for medical students and junior residents commencing their theatre experience.

The New Public Health: An Introduction for Midwives, Health Visitors and Social Workers. By Fred Grundy, M.D., M.R.C.P., D.P.H.; fifth edition; 1960. London: H. K. Lewis & Co. Ltd. 8¾" × 5½", pp 224, with illustrations. Price: £1 1s. net (English).

THIS book, by the Professor of Preventive Medicine of the University of Wales, provides a compact, though comprehensive, survey of the health and welfare services of Great Britain. It succeeds the author's well-known "A Handbook of Social Medicine", which, after passing through five editions, was rewritten and published under its present title in 1949. This was due to the great changes consequent upon the introduction of the *National Health Service Act* and other important legislation. Though the work is intended especially for the education of midwives, social workers and health visitors, it serves as a useful and up-to-date introduction to the subject for a much wider public.

The author, though attempting "to avoid sacrificing accuracy for simplicity", has compressed a large amount of information in his pages, and has skilfully summarized the pertinent legislation. A concise review is provided of local and central government organization and administration, the *National Health Service Act* and the organization of the medical services, social security and national insurance, the local health department and the medical and welfare services of local authorities. Chapters are also included on the prevention and control of infectious diseases, the arithmetic of health and disease, social medicine and environment, and other subjects of importance. A list of useful references is appended. This edition, the fifth, has been brought up to date, particularly in regard to health statistics and to recent extensive alterations in legislation.

Clinical Applications of Cardiopulmonary Physiology. By M. Henry Williams, Jr., M.D.; 1960. New York: Paul B. Hoeber, Inc. 9¾" × 6", pp. 246. Price: $7.50.

THE aim of this book is "to outline normal cardiopulmonary physiology, to point out the areas that may be assessed by physiological techniques, and to indicate the bearing that such studies may have on the diagnosis, evaluation, and treatment of patients with cardiopulmonary disease". "Outline", "point out", "indicate", are words which disarm criticism in a review, especially when a further paragraph in the preface is devoted to specified limitations and qualifications and to an indication of what the book is not. Unfortunately, one looks in vain for a statement indicating to whom the work is directed. It may be assumed that it is not for the expert, an assumption which is confirmed by perusal. The simplicity of the exposition in general is laudable if the work is intended for the student; but this leads to ludicrous propositions ("The lung pump is basically different from the heart pump in that air is pumped back and forth through one airway into and out of a large alveolar space"), to extreme dullness (". . . expansion of the chest causes the lungs to expand so that air flows into the alveoli. Contraction of the chest and lungs during expiration causes air to flow out of the alveoli") and to frankly misleading statements due to over-simplification (compliance "provides an objective index of lung stiffness", its relation to ventilated lung volume being ignored). Teachers in this country will not appreciate their students reading that the "accurate diagnosis and evaluation of [valvular insufficiency] depend upon the injection of a foreign substance into the cardiac chamber or vessel distal to the lesion" and its recovery proximally. Even though this general statement (it is repeated specifically in relation to aortic, tricuspid and mitral incompetence) occurs in a chapter on the evaluation of structure by physiological

techniques, it is inexcusable to give these techniques such emphasis to students at the expense of clinical signs. The physician's experience would allow him to view the statement in proper perspective, but we doubt whether he will have got beyond the elementary passages previously quoted.

There are other views set out in this book to which exception may be taken. "Conventional indexes" derived from a spirogram do not provide an index of airway calibre (page 36). The value of a classification of heart failure which has, as one "general cause", "reduced effective blood and/or red cell volume" and, as examples of this, hæmorrhage and anæmia (representing acute and chronic "specific causes" respectively) eludes us (pages 63 and 64). "The diffusing capacity is not reduced in uncomplicated asthma" occurs on page 102; this is (rightly) modified somewhat on page 103, and contradicted clearly in the table on page 104. To state that bullous emphysema is a different disease from that of bullæ occurring in chronic obstructive emphysema is a complicated and misleading way of stating that localized bullous lesions may occur in otherwise normal lungs (page 124). Two out of the three stated purposes of breathing exercises are unphysiological, on the author's own statements, and the third one is a contradiction of the first (page 113). By contrast, some of the sections on gas exchange, especially in regard to carbon-dioxide retention in emphysema, are in advance of those found in other reviews, and some of the sections on functional disorders in specific clinical syndromes are useful summaries for the student and the general physician.

We are forced to conclude that this book is unsuitable for the undergraduate student mainly because its perspective is wrong, and for post-graduate students and the general physician because its simplicity is at times irritating and at times misleading. For these, and for the expert, better works are available. If it is written for the general practitioner with an interest in recent advances in this field, but with no close acquaintance with newer techniques and physiological concepts, then many of these criticisms may reasonably be withdrawn. It will, as the publisher's blurb suggests, help him to decide when special investigations are indicated. The style is clear, the diagrams are helpful, the approach is comprehensive and the references are reasonably well chosen.

The book is well produced, as would be expected at this price. Readers who feel that not one, but two, mistakes in the spelling of Poiseuille's name throughout the book throw doubt on the accuracy of the remainder of the text, will not, of course, get past page 5, where the error occurs three times.

Parkinsonism: Its Medical and Surgical Therapy. By Irving S. Cooper, M.D., Ph.D., F.A.C.S.; 1961. Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications Ltd.; Toronto: The Ryerson Press. 11″ × 8½″, pp. 250, with many illustrations. Price: £6 12s. (English).

THIS book is the latest and most comprehensive of Cooper's numerous publications on methods for the relief of tremor and rigidity. He has now operated on over 1500 patients for Parkinsonism, so that his opinions are backed by an undeniably extensive experience. The development of surgery in these conditions is outlined and correlated with the anatomical and physiological studies.

The detailed operative techniques now being used by the author in chemopallidectomy and chemothalamotomy are fully described and illustrated with numerous diagrams, drawings and X-ray films. The results with these methods have been impressive, effective relief being achieved for 80% of the patients operated upon, and risks have been low. It should be noted, however, that only 30% of the sufferers seen were considered suitable for surgery.

The radiological, anatomical and clinical features are correlated in considerable detail, and then numerous representative clinical records are presented and evaluated.

The book has been attractively prepared and the data are well documented. Although a good deal of its contents have already appeared, it should be of wide interest and of especial value to neurological specialists responsible for the treatment of Parkinsonism.

French's Index of Differential Diagnosis. Edited by Arthur H. Douthwaite, M.D., F.R.C.P.; eighth edition; 1960. Bristol: John Wright & Sons Ltd. 10″ × 6½″, pp. 1124, with many illustrations. Price: 126s. (English).

THE first edition of this comprehensive index was published in 1912, and it has maintained its popularity throughout the years. It now appears in its eighth edition, completely revised: obsolete material has been deleted, whilst many new monographs and illustrations have been added.

This index was designed to assist the practitioner in the differential diagnosis of various diseases by discussing the prominent symptom in a given case and thereby proceeding to a diagnosis by differentiating between the various diseases to which this symptom may be due.

The index is easily referred to, as the various symptoms are arranged in alphabetical order, and it covers the whole field of medicine, surgery, gynæcology, ophthalmology, dermatology and neurology. A very complete general index at the end gathers these symptoms together under headings of the various diseases in which they occur, and should be freely referred to.

Treatment, pathology and prognosis are dealt with only in so far as they bear on differential diagnosis.

The book is extensively illustrated, there being a total of 744 illustrations, 216 of these being in colour. The list of contributors includes the names of many world-famous teachers. This is a book which will be of great service to students, interns and practitioners, young and old, in general practice or the specialties. It is, as usual, well presented on first-quality paper, and is a credit to the publishers. It is highly recommended.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Clinics in Electrocardiography", by Dale Groom, A.B., M.D., M.S. in Med., F.A.C.P.; 1960. Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 10″ × 6¾″, pp. 152, with illustrations. Price: 64s. (English).

"Fetal Electrocardiography: The Electrical Activity of the Fetal Heart", by S. D. Larks, B.S.E.E., M.S. (E.E.), Ph.D.; 1961. Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 10″ × 6¾″, pp. 110, with illustrations. Price: 52s. (English).

"Radiopaque Diagnostic Agents", by P. K. Knoefel, M.D.; 1961. Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9″ × 6″, pp. 158, with figures. Price: 54s. (English).

"Mortuary Science", by Frederick C. Gale, with a foreword by T. J. Curphey, M.D.; 1961. Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9″ × 6″, pp. 214, with many illustrations. Price: 76s. (English).

"An Approach to Community Mental Health", by Gerald Caplan, M.D., D.P.M.; 1961. London: Tavistock Publications. 8½″ × 5½″, pp. 262. Price: 25s. (English).

"Pathogenesis and Treatment of Cerebrovascular Disease", seventh Annual Scientific Meeting of the Houston Neurological Society, Texas Medical Centre, Houston, Texas, compiled and edited by W. S. Fields; 1961. Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9″ × 6″, pp. 562, with illustrations. Price: £6 (English).

"Optics: An Introduction for Ophthalmologists", by K. N. Ogle, Ph.D.; 1961. Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9″ × 6″, pp. 266, with figures. Price: 70s. (English).

"The Surgical Treatment of Intracranial Meningiomas", by C. S. MacCarty, B.A., M.D., M.S. in Neurologic Surgery; 1961. Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9″ × 6″, pp. 70, with illustrations. Price: 36s. (English).

"A Biochemical Basis of Multiple Sclerosis", by Roy L. Swank, M.D., Ph.D.; 1961. Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9″ × 6″, pp. 88. Price: 40s. (English).

"The Management of Pediatric Practice: A Philosophy and Guide", by H. C. Thompson, M.D., and J. B. Seagle, M.S., M.D.; 1961. Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9″ × 6″, pp. 172. Price: 60s. (English).

"Orthopædic Approaches: A Stereographic Manual, Section 1: Lower Extremity", by J. J. Joyce, III, M.D., B.A., and Michael Harty, M.A., M.B., M.Ch., F.R.C.S. (Eng.); 1961. Baltimore: The Williams & Wilkins Company. 10″ × 7″, pp. 80, with illustrations and 18 stereographic reels Price: £15 8s.

The Medical Journal of Australia

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DEVELOPMENTS IN PSYCHIATRY IN NEW SOUTH WALES.

ELSEWHERE in this issue we publish the interim report on preventive psychiatry prepared by the Health Advisory Council of New South Wales, which was recently made public by the State Minister for Health, the Honourable W. F. Sheahan. It is described by the Chairman of the Council, Dr. C. J. Cummins, in the preamble to the report as it was presented to the Minister, as the first of a series of reports by the Council on an integrated mental health programme for the State of New South Wales. It deals with one aspect of preventive psychiatry—namely, the establishment of a comprehensive community mental health service—and it recommends principles which the Council considered that the State Government might adopt as policy in the foundation of such a service. Dr. Cummins goes on to point out that as a corollary to these principles, the function of the mental hospital system in New South Wales, and of individual mental hospitals, will require redefinition to conform with the concept of a total integrated mental health programme. In this respect the report advances certain proposals for the development of the Parramatta Mental Hospital and the Callan Park Mental Hospital. A proposal is also advanced for an Institute of Psychiatry to provide teaching and research facilities for the faculties of medicine of both the University of Sydney and the University of New South Wales. Not least it encourages the establishment and development of psychiatric centres at general hospitals and, in particular, teaching hospitals.

This report has been generally welcomed. It is apparent that more is to come in due time, so that it would be pointless to refer to what the report leaves out. The important thing is that positive proposals are being put forward by a responsible official body, after consultation with interested organizations and individuals, to develop psychiatric services in New South Wales along modern lines. This is long overdue, as ideas in the field of mental health have been undergoing radical changes for some time now. These changes involve such major matters as the principles of construction and management of mental hospitals, so that putting them into effect requires time and money in substantial amounts. It is encouraging to note that Mr. Sheahan, when he made the report public, stated that it was "a most informative and exciting document", exciting in the sense that it drew the attention of the public to the neglected section of the people—the mentally ill and geriatric patients. He commented that if the public wanted better treatment for this section of the community, it must be prepared to pay for it. More important, he said that what was embodied in the report would be his policy, and he hoped that any other Minister would also adopt the principles of the report. It is to be hoped that this will not be forgotten. Not that we question Mr. Sheahan's sincerity, for he is obviously enthusiastic about the report and has undertaken to do something about matters of priority without undue delay. But Ministers of Health come and go, and continuity of policy and of enthusiasm for translation of policy into action is essential if governments of the present and of the future are to be kept active in this vital and needy field. The report comes from a responsible source and is much too informed and constructive to be pigeon-holed. The only worse thing that could happen to it would be to be kept in view, constantly admired and never implemented.

THE AUSTRALASIAN MEDICAL STUDENTS' ASSOCIATION.

IN each of the medical schools of Australia and New Zealand a students' society has existed since the early days of the school. Many of the societies have long felt the need of combining in some form, and attempts have been made in the past by the Sydney and the Melbourne Medical Students' Societies to form a national association. However, it was not until last year that the University of Queensland Medical Society, with the support of the other medical students' societies, took the initiative and held what was to be the first convention of the Australasian Medical Students' Association in Brisbane during the May vacation of 1960. The medical students' societies of the Universities of Queensland, Sydney, Melbourne, Adelaide and Western Australia were the foundation members of the association, and Mr. David Scott, a fourth-year medical student from the University of Queensland, was elected its first president. During the first year of its existence, despite some inevitable "teething troubles", the Australasian Medical Students' Association was very active. Soon after the Brisbane convention a statement was released to the Press throughout Australia dealing with the association's policy on the limitation of numbers at Australian medical schools. This policy was that while the association was anxious that more medical schools should be established, so that those who wanted to take a medical course and who had a reasonable chance of passing might do so, it nevertheless supported the principle of limitation of numbers within each school. At the beginning of July, 1960, the executive secretariat was handed over to the Melbourne Medical Students' Society, and Mr. Bernard Carroll, Mr. John McEncroe and Mr. John Woodward, all fourth-year medical students, took office as President, Honorary Secretary and Honorary Treasurer respectively. They obtained reports on the operation of the Commonwealth Scholarship Scheme in each university and critically reviewed the scheme as it served medical students. A similar survey of student health services within Australian universities was also

undertaken. The second annual convention of the association, held in Melbourne in May, 1961, is reported elsewhere in this issue. After twelve months in office the secretariat from the Melbourne Medical Students' Society handed over the reins of office to the Sydney University Medical Society, and the present office bearers are Mr. Peter Wilenski (President), Mr. John Hilton (Honorary Secretary), and Mr. Donald Chisholm (Honorary Treasurer).

The aims of the Australasian Medical Students' Association as set out in its constitution are: to serve and represent the medical students of Australasia and to promote cooperation and understanding among them; to encourage the interchange of ideas in all fields of medical education and practice and to uphold the ideals of university medical teaching; to facilitate cooperation between the medical student and the medical profession, and where necessary to cooperate and affiliate with other bodies having similar aims. At the national student political level the association is one of the affiliated faculty bureaux of the National Union of Australian University Students. It has received considerable assistance, financial and otherwise, from that union. On the international level negotiations with the International Federation of Medical Students' Associations have resulted in the affiliation of the Australasian Association with the International Federation, and Australia is to be, most appropriately, the centre for the South-East Asian countries. Negotiations with the medical students' society of the University of Otago in New Zealand are expected to result in their affiliation with the Australasian Medical Students' Association in the near future. Projected plans of the association for the coming year include efforts to stimulate interest in extra-curricular activities among medical students and to include non-medical subjects in the early years of medical courses, the establishment of a scheme whereby medical students can obtain a trade reduction on books and instruments, liaison with the Medical Education Subcommittee of the Australian Universities Commission and the publication of a regular A.M.S.A. newsletter. Above all the association has expressed its wish to develop in a similar fashion to that of its British counterpart, the British Medical Students' Association. This association was founded in 1942, and its membership is said to include over 90% of the medical students in Great Britain. According to a statement published in 1958,[1] it is purely a professional organization, providing a means of communication between medical students in the different universities and hospitals, and also between British students and those in other countries. It presents the medical student's point of view to the medical profession, to government departments and to other interested bodies. It arranges clinical and pre-clinical conferences and schools from time to time, which are in addition to local activities arranged by the constituent organizations. It publishes the *British Medical Students' Journal* once a term and an annual list of vacation appointments for members requiring work in hospitals during vacation. It is represented on those committees of the British Medical Association that deal with matters affecting students and newly-qualified doctors, and also maintains a happy liaison with the College of General Practitioners with representatives sitting on the undergraduate education committee of the College. Following this example, the Australasian Medical Students' Association is particularly anxious to establish and maintain the closest possible link with the medical profession in Australia, and hopes for some form of affiliation with the Australian Medical Association which is about to be formed. We feel sure that all members of the medical profession will welcome the formation of the Australasian Medical Students' Association and its desire to establish friendly and effective relations with the organized medical profession. Suitable machinery for such an arrangement will need to be worked out, but it is obvious that it can only be for the good of all concerned.

[1] *Brit. med. J.*, 1958, 2: 630 (September 6).

Comments and Abstracts.

THE SO-CALLED ANONYMOUS MYCOBACTERIA.

THERE are few things more rewarding than the study of history. This is especially true of the history of scientific discoveries in the field of medicine. It is inspiring to recapture the victorious flash of original thought; on the other hand it is salutary to realize that findings which at first appeared to be simple and clear-cut are often seen in the light of subsequent work to be clouded by many complexities. C. Xalabarder,[1] discussing recent studies of the unclassified so-called "atypical" mycobacteria, considers that the approach of some workers in this field is erroneous and misleading. It stems, he believes, from the oblivion into which the history of bacteriology has sunk at the present moment, for it is only unfamiliarity with that history which can explain the survival of the erroneous and anachronistic theory of "monomorphism" which was postulated by Koch. "These unclassified organisms", writes Xalabarder, "are referred to as 'anonymous' or chromogenic because they do not all possess the same characteristics as the human tubercle bacilli. In general, they are non-pathogenic for guinea pigs and exhibit poor susceptibility to antimicrobial drugs. Many of them form pigments and this property has been used in part as the basis for classification." In a masterly review of the history of the mycobacteria, Xalabarder proceeds to attack the validity of these criteria as a basis for classification. He does this by considering the earliest or most outstanding investigations available. According to Koch, the tubercle bacillus invariably presented the following characteristics: (i) development was slow (four to eight weeks) and took place only in special media; (ii) the colonies were dry, squamous, friable and whitish to creamy in colour; (iii) it could not tolerate changes in temperature; (iv) it was invariably pathogenic and parasitic in character. Other properties that appear to be more common in pathogenic strains have been added since Koch's time—such as cord formation, niacin synthesis, specific cytochemical reactions and so on. It is significant that the great majority of the characteristics of the pathogenic mycobacteria are biological deficiencies, and therefore possibly the results of adaptation. Of Koch's four criteria, the first, slow growth, can no longer be regarded as an invariable property of the tubercle bacillus for it grows very rapidly indeed on many of the newer media. Pigmentation, too, is a variable property and often dependent on the judgement of the individual observer. The third criterion, inability to tolerate changes of temperature, is shown by some of the saprophytes and unclassified mycobacteria. Finally, the virulence of mycobacteria has been shown to vary. Since 1891 it has been known that tubercle bacilli can be made less virulent by serial inoculation in the same medium after long periods

[1] *Amer. Rev. resp. Dis.*, 1961, 83: 1.

of time. The presence of fatty acids or the action of heat may lessen their virulence; as also may variations in culture media. Virulence may be lessened by passage through reptiles or frogs or enhanced by repeated passage through highly susceptible animals. In fact, as this writer points out, the only constant characteristic of the pathogenic mycobacteria is their extreme plasticity and adaptability to a number of environments. This adaptability is exercised by them under the influence of antimicrobial drugs, producing changes in morphology and in virulence.

It is impossible to do justice to this excellent review in a brief comment such as this. It should be read in full by all who are interested in the tubercle bacillus; indeed by all who have a concern for the tuberculous patient. For this is not merely a laboratory curiosity. There is a tendency to place the "anonymous" mycobacteria in a class apart and to affirm that the lesions they produce in man are not tuberculous and are therefore of no epidemiological significance. A monograph on "The Anonymous Mycobacteria"[1]) was reviewed in these columns recently. A concern for the epidemiology of tuberculosis is the motive behind Xalabarder's review. His conclusions deserve to be quoted in full:

> Bacteriologists have established their systems of classification on the basis of assigning fixed, precise, and immutable characteristics to each group of organisms. This was necessary for didactic purposes in the purely descriptive stage of bacteriological research. However, as the agreement was unilateral, the result was that the bacteria, not aware of this convenient human arrangement, have continued their normal biologic processes, which consist in a steady evolution and adaptation to the greatest variety of environmental conditions, so that now there is great discrepancy between the real state of affairs, and that envisaged by our well-intentioned blueprints. In order to overcome this difficulty, recourse to two subterfuges appeared necessary; occasional modification of the taxonomic pattern and, in the case of tuberculosis, formation of a separate group containing all of the mycobacteria which do not play the game according to the rules fixed by the committee, dubbing them "atypical" acid-fast bacilli and segregating them into a group apart from all other mycobacteria. This procedure, far from clarifying matters, has led to considerable confusion and mistaken conclusions dangerous to the interests of epidemiology. Pergola protested against all of this fifteen years ago in the following statement: "There is no justification for the creation of a type of atypical bacilli, since their lack of a pathogenic power depends on other factors and not on the bacillus itself."

METASTASES OF THE LATERAL PELVIC WALL.

AT a scientific meeting of the Royal College of Obstetricians and Gynæcologists, W. G. Cosbie opened a symposium on "The Pathology and Treatment of Malignant Glandular Metastases of the Lateral Pelvic Wall" with a paper by himself and W. Anderson[2] of Toronto. In this paper they state that they consider involvement of regional lymph nodes to be a mechanical process, malignant cells being carried in the lymph stream. Host resistance may be encountered in the lymph nodes, but cancer cells are not destroyed by lymphoid tissue. Cosbie and Anderson believe that arrested cancer cells in lymph glands profit by their location in a nutrient focus. The growth may be confined within the capsule of the lymph gland for a variable time, but sooner or later groups of glands tend to coalesce as the result of extracapsular infiltration and occlusion of the connecting lymphatics. Blood-borne dissemination may follow the extension of neoplasm to lymph glands, the filter action of the latter becoming a nidus for further spread. Neither Wertheim or Schauta stressed the need to remove lymph nodes in their classical operations. However, Victor Bonney in 1941 stressed the importance of lymph-node spread and of wide lymph-node removal in the treatment of uterine cancer. J. V. Meigs in 1951 demonstrated that radical hysterectomy and pelvic lymphadenectomy could be performed with a very small operative mortality and concluded that adequate surgery provided the only means of controlling involved lymph nodes. Taussig in 1943 found 26·8% involvement of lymph nodes in patients submitted to transperitoneal lymphadenectomy after radiotherapy. Only 21% of these patients survived for five years. Morton in 1947 noted lymph-node involvement in 35% of patients treated by primary surgery and in 11·4% when surgery was performed after radiation. Cosbie and Anderson state that the justification of the extensive exenteration operations of Brunschwig is the fact that in only 50% of cases is there macroscopic evidence at autopsy of cancer spread beyond the pelvis. Parsons in 1959 reported a five-year survival rate of 24% in exenteration cases. In this series 50% of patients whose lymph nodes were not involved survived five years, but none survived when the nodes were involved.

Having thus surveyed the field, Cosbie and Anderson appear to come to the conclusion that lymphadenectomy in the treatment of pelvic cancer has had little effect on the survival rate when the results are compared stage by stage with those of hysterectomy combined with radiotherapy. They then point out that during the last 20 years radiotherapy for pelvic cancer has become much more efficient, and quote the experiences of the Ontario Cancer Foundation. A review of over 4000 cases of cervical cancer in 1959 showed an improvement in the five-year survival rate from 33·3% to 45·6% during this period. The greatest relative improvement occurred in Stage II and Stage III lesions. After quoting the results of radiotherapy recently reported from several other centres, and referring to the cytological studies of the Grahams, Cosbie and Anderson end by stating that it is apparent "that our concept of the control of malignant disease originating in the female pelvis must not be limited to any solitary facet of the problem irrespective of its apparent immediate importance".

In the second paper of the symposium, A. D. Campbell[2] begins by stating that the inability to improve appreciably the survival rate, no matter what type or combination of types of treatment is used, demands a reappraisal of the problem. He reflects that consideration of the pathological processes along with the treatment employed and the results obtained seems the only way to improve survival rates. He draws attention to certain anatomical and biological characteristics of the lymphatic system: lymph nodes are abundant in the young and sparse in the aged; natural regression of the activity of the endocrine system which occurs at about the fifth decade may account for the relatively slow spread of carcinoma in patients in this age group; no two individuals have precisely the same lymphatic arrangement; the factor of host response defies clinical assessment, and it is not possible to assess cancerous involvement of lymph nodes by physical examination; retrograde lymphatic spread of cancer is recognized and forward spread to successive nodes is not always the rule. It has been shown by several workers that the size of the primary growth and the stage of cancer do not bear a direct relation to the degree of lymphatic involvement. The histological pattern of cells in a malignant tumour may give little indication of its proclivities. Cancer cells are thought to be genetically different from other cells of the host and carcinomatous cells differ within a tumour mass itself. Campbell and his colleagues at Montreal have directed their attention towards improvement of radiotherapeutic technique. Radical surgery in the treatment of carcinoma of the cervix is reserved in their clinic for patients with recurrence after irradiation. They have the impression that the survival of patients with spread of growth to lateral pelvic nodes has improved since the introduction of treatment by radioactive cobalt with cæsium bombs. A new type of semi-rigid applicator for intracavity irradiation is described and illustrated. This provides a fixed relationship of vaginal and intrauterine radium sources and obviates the necessity of

[1] MED. J. AUST., 1961, 1: 490 (April 1).

[2] *J. Obstet. Gynæc. Brit. Emp.*, 1960, 67: 709 (October).

[2] *Ibidem*, page 714.

vaginal packing. When the lateral pelvic lymph nodes are involved in carcinoma of the body of the uterus, it is thougnt that the paraaortic nodes are potentially involved and radical surgery would not encompass the disease. Campbell considers that lymph nodes can be removed surgically, but that malignant cells probably remain in the adjacent cellular tissue. The merit in surgery probably lies as much in the destruction of lymphatic channels as in the removal of nodes. He suggests that adequate irradiation provides a similar obliteration of the lymphatic channels.

In the third paper of the symposium, A. M. Hill[1] of Melbourne presented a study of 507 patients who underwent pelvic lymphadenectomy for uterine cancer at The Royal Women's Hospital, Melbourne, in the 10 years up to the end of 1959. Of the total, 415 had cervical cancer with an incidence of 24% pelvic lymph-gland metastases, and 92 had carcinoma of the body of the uterus with 11% node involvement. Prior to surgery, 79% of patients with cervical cancer and 66% of those with cancer of the uterine body received radical radiotherapy. Among the 100 patients with cancer of the cervix who had pelvic lymph-gland metastases, in only 53 was this suspected at the time of operation. The criteria of malignancy in lymph nodes were: hardness, enlargement, irregularity or fixity. The glands most commonly involved were the external iliac and obturator nodes and the least commonly involved was the ureteric gland. Metastases in more than one group of glands occurred twice as frequently among patients who subsequently died as among the five-year survivors. Hill considers that the most striking finding in the study is the infrequency of malignant infiltration of the parametrium (3·7% among patients with cancer of the cervix). Among 35 patients considered to have parametrial involvement and classified as Stage II cases, malignant spread was found in only two. These findings are in marked contrast with the 24% incidence of lymph-node metastases, and are in accord with Hill's clinical experience that parametrial infiltration in patients with uterine cancer is more often inflammatory than neoplastic. The clinical staging of growths with suspected parametrial extension is considered to be correspondingly inaccurate. In the operative treatment of invasive carcinoma of the cervix, Hill considers it fundamental to remove the pelvic lymph glands if this is technically possible. They may be involved yet look normal, and if involved nodes are left they may later cause intractable pain. Patients with cancer of the lower half of the uterine body or with adenoacanthoma should have routine removal of lymph glands, as these lesions behave like cervical cancer as regards lymph-node metastasis. The five-year survival rate of patients with cervical cancer and lymph-gland metastases was 26%, a figure one-third that of patients whose lymph glands were free of cancer. In cases of cancer of the uterine body with lymph-gland involvement the outlook is also grave. Hill concludes with these three observations: (i) An attempt should always be made to remove the regional lymph glands of the pelvis in the surgical attack on invasive cervical cancer or cancer of the upper half of the body of the uterus. Even if the paraaortic glands or large vessels are involved, glandular excision should be attempted. (ii) In view of the infrequency of malignant involvement of the parametrium, its clearance to an extent risking permanent vascular or urinary-tract damage is unjustified. (iii) Fractional curettage in cases of carcinoma of the body of the uterus is mandatory in order to assess the part of the uterus involved by growth and the histology of the neoplasm.

Consideration of these three papers, by authorities from three different centres in Canada and Australia, undoubtedly, and perhaps inevitably, leaves the reader with a feeling of inconclusiveness. The Canadian authors studiously avoid committing themselves to any definite proposition. The main point on which they agree is that, while there have been great improvements in technique, in both surgery and radiotherapy, the long-term outlook for the patient has changed depressingly little over the decades. Much more can be done to help the patient than was possible 30 years ago, but, in the final result, most patients who have involved lymph nodes when first investigated still die of their cancers. Hill at least firmly believes that, in the operative treatment of invasive cervical cancer and of some cancers of the uterine body, lymphadenectomy should be undertaken when this can be done with safety, and gives categorical reasons for this opinion.

[1] *Ibidem*, page 717.

SHORTER ABSTRACTS.

OBSTETRICS AND GYNÆCOLOGY.

HÆMOLYTIC DISEASE OF THE NEWBORN. Alan Moncrieff, *J. Obstet. Gynæc. Brit. Emp.*, 1960, 67: 740-741 (October).

AT a scientific meeting of the Royal College of Obstetricians and Gynæcologists the author introduced a session on hæmolytic disease of the newborn with a short survey of certain theoretical considerations. Stating that the clinically important hæmolytic disturbances in the baby are due to the rhesus factor, he raised the question as to why hæmolytic disease of the newborn does not happen more often, and may not happen at all, even if the stage appears, genetically, set for its occurrence. The Rh-negative state occurs in 15% of persons of European stock, and 12% of all marriages are between Rh-negative women and Rh-positive men. Some fathers are, of course, heterozygous for the Rh factor, but even so the incidence of 1 in 200 pregnancies for Rh incompatibility is small. The author thinks that women vary in their degree of sensitivity to and response to Rh-positive red cells. The infant also varies in the severity of the disturbance caused by Rh incompatibility. It has been estimated that only one half of Rh-negative recipients of Rh-positive cells develop antibodies. The Rh-negative mother is less likely to be sensitized by Rh-positive cells when the partners are incompatible in the ABO system. Further, 15% to 20% of Rh-positive infants born of sensitized Rh-negative mothers have no clinical illness, although the result of the Coombs test is positive. Prophylactic treatment for hæmolytic disease of the newborn by giving "Rh hapten" or cortisone to sensitized pregnant women has given disappointing results. The possibility of using an artificial blood group chimera, i.e., a graft of fœtal tissue, has been suggested. Experimental work on monkeys has been carried out on these lines—the umbilical vein of the fœtal monkey is exposed by hysterotomy, hæmopoietic tissue is injected, the uterus is then closed and the pregnancy allowed to proceed. The diagnosis of Rh hæmolytic disease of the newborn depends on demonstrating the presence of maternal antibodies and the finding of an Rh-positive baby with a positive result to the Coombs test. If antibody testing has not been performed, severe jaundice in the newborn presents a diagnostic problem, and ABO incompatibility, congenital syphilis, toxoplasmosis, cytomegalic inclusion disease and congenital leukæmia must be considered. The author does not favour amniotic taps for bilirubin estimation as a diagnostic procedure. He considers there is a definite risk of puncturing the placenta, which may result in the passage of fœtal cells into the maternal circulation, with a sudden and damaging rise of antibody titre.

HÆMOLYTIC DISEASE OF THE NEWBORN. F. Stabler, *J. Obstet. Gynæc. Brit. Emp.*, 1960, 741: 744 (October).

IN a paper read before the Royal College of Obstetricians and Gynæcologists, the author discusses hæmolytic disease of the newborn as a community problem from the point of view of prediction, prompt recognition of non-predictable cases, and efficient treatment in well equipped centres. He describes how the problem has been tackled in the counties of Durham and Northumberland since 1949. Several factors are necessary for the establishment of good results in a community. The disease is for the most part predictable, and a prediction rate of 95% should be aimed at. For unpredicted cases there should be a quick and simple means of selecting those babies who require treatment. The efficient performance of the treatment decided upon is the final objective. The author believes that in a well organized community service following such principles the mortality of live-born affected babies should approach the figure of 2%. In 1957 the general mortality for England and Wales in

such cases was 12·5%, whereas in Durham and Northumberland it was 3·5%. No satisfactory test is available for the prediction of ABO hæmolytic disease or for immunization due to rare sub-groups of the Rh factor (approximately 5% of cases). Prediction rates in the North-East Region of England were 86% to 88·5% in the years 1956 to 1959. Unpredicted cases occur at the rate of about one per 40,000 live births in these counties. Among the non-predictable patients, detection early after birth is established by a routine Coombs test on cord blood of babies of all Rh-negative mothers, and by referring to hospital all babies who show jaundice within 24 hours of birth, and all babies deeply jaundiced within the first week of life. The total of predicted and "picked up" cases ranged from 92% to 96·8% during 1956 to 1959. During these four years there was a total of 1139 babies with hæmolytic disease of the newborn, of whom 139 were stillborn and 1000 were treated. The criteria for selection of cases for treatment are now fairly standardized, and selection is therefore less important than effective prediction and efficient treatment. The author gives the indications for early exchange transfusion as follows: a cord hæmoglobin value of less than 14·8 grammes per 100 ml., whatever the bilirubin level; a cord bilirubin level of more than 4 mg. per 100 ml., whatever the hæmoglobin value; a cord hæmoglobin value of 14·8 to 17·7 grammes per 100 ml. associated with a bilirubin level of 2·8 mg. per 100 ml. or more. Premature induction of labour is not practised as a routine in this area, but if the husband is homozygous and the woman has already had in intra-uterine death or hydrops from hæmolytic disease of the newborn, labour is induced at 35 or even 32 weeks.

The author maintains that if the conditions which obtain in Northumberland and Durham prevailed throughout England and Wales, 300 out of the 400 deaths which occur annually from hæmolytic disease of the newborn could be avoided. In addition to efficient prediction of likely cases and prompt recognition of unpredicted cases, he advocates that all patients needing exchange transfusion should be treated at large central hospitals which are fully equipped for the purpose, and which have a team of workers experienced in the management of the condition. The proper management of hæmolytic disease is not a matter of the skill and knowledge of one person, but of the coordination of the activities of a large number of people.

TRANSVAGINAL REGIONAL ANÆSTHESIA. A. J. Kobak and M. S. Sadove, *Amer. J. Obstet. Gynec.*, 1961, 81: 72 (January).

THE authors present a combined method of regional anæsthesia, paracervical and pudendal, for the relief of painful uterine contractions in the first and second stages of labour and the terminal phase of labour. The site of injection for the paracervical block is at the junction of the lateral walls of the cervix with the vagina at the three o'clock and nine o'clock positions. Approximately 10 to 14 ml. of anæsthetic solution are injected on either side. When paracervical anæsthesia develops most patients become unaware of uterine contractions; pudendal block is done when paracervical block is effective. Relief of pain was obtained in all of the 100 patients who received regional transvaginal anæsthesia. Of 98 cases with cephalic presentations, in 48 delivery was spontaneous and in 50 delivery was by forceps; 15 of these were cases of mid-forceps delivery, and in nine rotation was necessary. Two infants were delivered as breech presentations. No other anæsthesia was required.

HYDRAMNIOS AND CONGENITAL ANOMALIES. F. Moya *et alii*, *J. Amer. med. Ass.*, 1960, 173: 1552 (August 6).

THE authors present a study of 74 patients with hydramnios at the Sloane Hospital for Women. They state that hydramnios has long been known to be associated with a high incidence of congenital anomalies and mortality in infants. In their present study they take two litres of amniotic fluid as the upper limit of normal, and cases of acute and chronic hydramnios are analysed together. Of the patients studied, 80% were multiparæ, five had twin pregnancies, 15 were delivered by Cæsarean section, and five had breech deliveries, all these figures being significantly greater than in the general patient population. There was also a high incidence of diabetes mellitus (14 cases) and pre-eclampsia (11 cases). Forty-one of the 79 infants were apparently normal, and all of these survived. Congenital anomalies were present in 21 (27%), a much smaller percentage than that reported in some other series. Ten of these anomalies were conditions which definitely interfered with fœtal ability to absorb fluid from the digestive tract in utero. In six other cases there was a macerated fœtus, and in a further eight cases various pathological abnormalities were present, including three cases of erythroblastosis. There were 23 perinatal deaths, including 16 stillbirths and seven neonatal deaths, an over-all perinatal mortality of 29%. Gastric catheterization and aspiration were used for all infants in order to diagnose congenital anomalies of the upper parts of the alimentary tract.

RUBELLA AND CONGENITAL ABNORMALITIES. F. Lock *et alii*, *Amer. J. Obstet. Gynec.*, 1961, 81: 451 (March).

THE authors report the results of a survey in North Carolina of 223 pregnant women, who had been infected by or exposed to rubella. Selection of cases was made at the time of rubella infection or exposure, and infections at all stages of pregnancy were included. The diagnosis of rubella was made by a physician when possible, and each child was examined by a trained medical investigator. The comparison group for the purpose of control was obtained by examination of the siblings. When typical rubella occurred in the first trimester of pregnancy, the incidence of fœtal abnormality was significantly higher than the incidence in the comparison group. With infection in the first four weeks of pregnancy, of a total of six cases, in three there was a fœtal abnormality; from the fifth to the eighth week there were 14 cases and abnormalities occurred in two; from the ninth to the thirteenth week there were 19 cases and abnormalities occurred in two. Abnormalities characteristic of rubella were not found in the absence of definite disease in this study. No conclusions could be drawn from the present material relative to the protective effect of gamma globulin. The spontaneous abnormality rate in the control group of siblings was 5·6%.

INDUCTION OF OVULATION WITH GONADOTROPINS. C. L. Buxton and W. Hermann, *Amer. J. Obstet. Gynec.*, 1961, 81: 584 (March).

THE authors present their preliminary findings on the stimulation of ovarian activity, including evidence of ovulation, by the intramuscular administration of human pituitary gonadotropin extracts. The extract used for injection was obtained from human autopsy material regardless of the age or sex of the subject. Patients were evaluated by means of basal body temperature charts, endometrial biopsy, vaginal smear, in one case culdoscopy and in another laparotomy. All patients except one control patient had been amenorrhœic either primarily or for from three to six years. They had various diagnoses. In seven cases of amenorrhœa there were two failures of therapy. The patients in the other cases responded to therapy by uterine bleeding from secretory endometrium, and had basal body temperature charts characteristic of progestational activity. It was therefore assumed that they had ovulated. One patient who was subjected to culdoscopy appeared to have at least three ovulation points on each ovary. It is impossible to say whether these ovulations were normal, but it is possibly of significance that none of the patients became pregnant. None of the patients who responded to therapy by menstruation and apparent ovulation continued to menstruate or ovulate subsequently.

THE INCOMPETENT INTERNAL OS. A. F. Lash, *Amer. J. Obstet. Gynec.*, 1961, 81: 465 (March).

THE author discusses the complications in the surgical treatment of 95 non-gravid patients, who had had repeated second trimester abortions due to incompetence of the internal os of the cervix, and 12 gravid patients (18 to 24 weeks) with imminent abortion. In the non-gravid group, the only complication was failure of the repaired cervix to retain a subsequent pregnancy; this happened in five patients. In this group the cervices were subsequently repaired once again. In the gravid patients, the Shirodkar operation was performed in the second trimester; complications were slipping of the suture in two patients, hæmorrhage requiring suturing and blood transfusion in one, infection in five, and rupture of the uterus in one. Infection is the major reason for complications and must be eliminated before operation in all cases. The author performs the Shirodkar type of operation only as an emergency procedure, and recommends that wedge excision of the scar or defect of the cervix should be performed when it is possible to operate during the non-pregnant state.

Public Health.

INTERIM REPORT ON PREVENTIVE PSYCHIATRY IN NEW SOUTH WALES.

THE following is the first of a series of reports by the Health Advisory Council of New South Wales on an integrated mental health programme for that State. It deals with the establisment of a comprehensive mental health service. It was presented to the N.S.W. Minister for Health, the Honourable W. F. Sheahan, on June 5, 1961, by the Chairman of the Health Advisory Council, Dr. C. J. Cummins.

MENTAL HEALTH.

Community thinking and attitudes in regard to mental illness have been conditioned over centuries. Consequently, it is not surprising that public enlightenment has lagged greatly behind the progress made in modern treatment of mental illness. Although in recent times steps have been taken to condition a new attitude by the community, there is still much to be accomplished by intensive and continuous widespread education. Accompanying this, however, must be a vigorous and constructive plan to provide adequate and accessible services for the community, together with modernization and improvement of existing facilities.

The modern approach to mental health is one of prevention, early treatment, re-socialization and establishment of adequate services to facilitate these. Time is needed to develop these services on a State-wide basis, but it is vital to formulate immediately a firm policy, with adequate planning, both short and long range.

Council has given consideration towards such a policy under the following headings: (*a*) Prevention. (*b*) Early intensive treatment. (*c*) Long-term treatment, rehabilitation and re-socialization. (*d*) Care of the aged. (*e*) Function of individual mental hospitals.

(a) Prevention.

Preventive psychiatry involves primarily health education, and secondarily, detection of mental illness in its earliest and preventible stage. Council is of opinion that prevention and early treatment of mental illness are fundamental to the success of the State mental health programme.

A comprehensive preventive programme will be of immediate benefit by reducing the incidence of mental illness and ameliorating its effects. The ultimate result will be to reduce the intake to, and the population of, mental hospitals.

Prevention in this context involves not only the health education of the community, but the better training of doctors, medical students, nurses and all others concerned in the field of general and social psychiatry.

The most fruitful field lies in health education of parents and children. This will enlarge the function of existing health services such as public health centres, school medical services, child guidance clinics, etc., and the Health Advisory Council will define proposals under these headings after it has further considered the organization of child psychiatric services and child mental health services. Another important preventive aspect lies in community and medical education directed towards the welfare and social needs of the aged.

The educational programme must be such as to embrace doctors, medical students and ancillary medical staff. General hospitals and, in particular, teaching hospitals must be included in this programme by the establishment of psychiatric, early diagnostic and treatment centres. No large general hospital renders a complete service unless it provides for short-term in-patient treatment for psychiatric cases.

This principle should be extended in all teaching hospitals to include provision also for satisfactory out-patient units and day hospital treatment, rehabilitation and community psychiatric services, although this is not necessarily the priority in which these services should be established. A comprehensive psychiatric service should also be established at selected non-teaching general hospitals according to population needs and distribution. The urgent need is to utilize existing facilities wherever possible.

Community psychiatric services, including out-patient departments, should be centralized in units close to teaching hospitals and the selected general hospitals and, preferably, within their precincts. Where these associations cannot be established by the use of existing facilities, new buildings will be necessary or suitable accommodation should be purchased.

(b) Early Intensive Treatment.

Facilities for early intensive in-patient treatment should be established so that patients will be encouraged to seek help. The service must be readily available to all, and must extend in principle through the general hospital system as well as in mental hospitals. Greater emphasis must be given to this function of a mental hospital than hitherto in the past.

(c) Long-Term Treatment.

Appropriate hospital and sufficient community facilities, such as hostels, sheltered workshops, after-care services, etc., must be available to provide lengthy psychiatric care for the more chronic forms of mental illness.

Rehabilitation facilities must be incorporated into community and hospital services to assist patients towards social adaptation and restoration to a useful and satisfying place in the community.

Council emphasizes that these facilities must be extended to the mentally retarded group as well as to those who are mentally ill. Rehabilitation in certain selected locations should extend to the prevocational and vocational fields.

Rehabilitation is a further function which merits greater emphasis in mental hospitals.

(d) Geriatric Patients.

Geriatric patients accommodated in mental hospitals should be classified with the objective of transferring suitable persons from mental hospitals to alternative accommodation external to mental hospitals. Where there is no appropriate alternative accommodation, special accommodation and facilities must be provided within mental hospitals. This accommodation should be sited, with the ultimate aim of degazettal.

(e) Function of Mental Hospitals.

The function of individual mental hospitals should be redefined in the light of the principles enumerated so that they will be put to the most useful and positive purpose.

INTEGRATION OF SERVICES.

Implementing these principles will involve modification of policy of organized health services administered by the State Psychiatric Services and the Public Health Divisions of the Department of Public Health and the general hospital programme of the Hospitals Commision of New South Wales, as follows:

State Psychiatric Services.

The Division of State Psychiatric Services should extend its activities into the community rather than concentrate almost exclusively upon the administration of mental hospitals. It should be the agency to stimulate, organize and coordinate community resources to augment and improve mental health facilities available to the public in need of assistance. This function should be catered for in the reorganization of its activities consequent upon the government policy for a uniform direction of public health and mental health professional services, in the creation of the combined posts of Director-General of Public Health and Director-General of Psychiatric Services.

Public Health Services.

Decentralization of Public Health Services should envisage the provision of in-patient and out-patient treatment in the base general hospital in each health district when there is no existing mental hospital. To further this end a psychiatrist and appropriate professional and secretarial staff should be attached to each relevant medical officer of health. The development of this policy, in association with the modification in health districts where there are mental hospitals (see below under "General Hospitals"), will enable a community mental health service to be extended to rural areas of the State.

General Hospitals.

Existing facilities of general hospitals should be used to establish out-patient and in-patient services. In certain country locations where there are existing mental hospitals, e.g., in the Cities of Goulburn and Orange, the psychiatric services at the general hospitals should provide for out-patient departments, serviced professionally by psychiatrists from the mental hospitals, as well as those in private

practice, if they are available. Early intensive in-patient treatment, in these circumstances, could be carried out at mental hospitals with economy of staff and services.

In country areas where there are no established mental hospitals, the prototype psychiatric unit at the general hospital should consist of an in-patient section for early treatment as well as an out-patient department, and psychiatric service to these units would be provided from the establishment of the medical officer of health.

IMPLEMENTATION OF POLICY.

Implementation of these proposals on a State-wide basis would, of course, necessarily imply long-range planning.

Immediate Projects.

The Health Advisory Council considers that planning to implement some of these principles could be commenced forthwith:

(i) *City of Parramatta.*

This centre is most suitable for the establishment of a comprehensive psychiatric service. The City of Parramatta is the hub of a district whose population is increasing rapidly. Parramatta District Hospital and the Parramatta Mental Hospital are in close proximity, and transport facilities to both are good.

The existing out-patient services at the Parramatta District Hospital and the Parramatta Mental Hospital should be coordinated into one service, associated with a community psychiatric centre, including a day hospital. These services should be located in a special unit in proximity to the Parramatta District Hospital.

The early treatment centre could be built on land associated with the Parramatta Mental Hospital. This unit should not form a part of the gazetted mental hospital. There is a section of land available which is ideal for the purpose.

There is adequate and suitable land available in the farm lands of the Parramatta Mental Hospital to establish a complete geriatric colony, including a geriatric hospital unit associated with the Parramatta District Hospital.

These, together with the Child Health Centre now being established in Parramatta by the School Medical Service, will provide an almost complete psychiatric service for the needs of the community of this city and district. The deficiency of a service for mentally retarded children could be remedied at a later stage when the overall State policy for the care of this section of the community is defined.

(ii) *Broughton Hall Psychiatric Clinic.*

The proximity of Callan Park Mental Hospital to Broughton Hall Psychiatric Clinic lends itself to the establishment of a complete adult psychiatric service, including an out-patient department and a psychiatric community unit, common to both hospitals. This unit should be established as an immediate priority, and would conform with the concept of the group of psychiatric components as a basis for an Institute of Psychiatry.

(iii) *Callan Park Mental Hospital.*

Consideration should be given to Callan Park Mental Hospital being divided into four functioning units as follows:

(i) to provide for early treatment through the admission centre and the admission wards;

(ii) to provide for long-term care and rehabilitation of patients in chronic stages of their mental illness;

(iii) to provide a geriatric unit including a hospital section for long-term care. This unit should be located in such an area within the grounds of Callan Park Mental Hospital whereby it can function independently, leading ultimately to degazettal.

(iv) to provide for neuro-psychiatric investigation and research under the ægis of the Cerebral Surgical Research Unit.

In planning the Callan Park/Broughton Hall project, early consideration will be given to provide a unit for the care of emotionally disturbed children and adolescents.

(iv) *Institute of Psychiatry.*

The concept of an Institute of Psychiatry by a grouping of the psychiatric units of the Broughton Hall Psychiatric Clinic and the reconstituted Callan Park Mental Hospital to provide teaching and research facilities for the medical faculties of both universities should be encouraged, and is a logical corollary of the proximity and function of this group of psychiatric units. The success of such an Institute can be anticipated from the results which have already been demonstrated by the association of the Sydney University, through the Professor of Psychiatry, with the Broughton Hall Psychiatric Clinic.

(v) *Psychiatric Services in Teaching Hospitals.*

In each teaching hospital provision should be made for a therapeutic trinity for early intensive in-patient treatment, an out-patient department devoted exclusively to psychiatry, and one or more community psychiatric centres, including day hospital or hospitals.

When staffing these units, advantage should be taken of the assistance which can be rendered by psychiatrists employed in mental hospitals, and such psychiatrists should be given adequate status on the staff of the teaching hospitals. The standard of total staffing of these units should be such as to ensure an adequate service to the community, and the out-patient department and the community psychiatric centre should be under the immediate supervision of a full-time psychiatrist.

(vi) *Staffing.*

The problems of recruitment of medical staff to mental hospitals are acute.

Expansion and modification of the existing scheme for appointing training Fellows in Psychiatry may provide a basis for attracting more medical men of quality into the specialty.

In view of the necessity to provide immediately adequate professional staff for the overall mental health programme, and particularly for the projects recommended, the Health Advisory Council considers that a further effort should be made to recruit psychiatrists throughout Australia and, if necessary, overseas under specific guarantees of employment.

Information should be disseminated widely concerning the proposed new mental health programme, and the remunerations paid to departmental psychiatrists should be reviewed in light of the failure to attract suitable candidates in previous recruiting campaigns. The services of part-time medical staff should be encouraged for out-patient services on a sessional salary basis.

SUMMARY OF RECOMMENDATIONS.

1. Principles.

(A) *Prevention.*

(*a*) Prevention and early treatment of mental illness are fundamental to the success of the State mental health programme.

(*b*) A comprehensive preventive programme will be of immediate benefit by reducing the incidence of mental illness and ameliorating its effects.

(*c*) Prevention in this context involves not only the health of the community, but the better training of doctors, medical students, nurses, and all others concerned in the field of general and social psychiatry.

(*d*) An important preventive aspect lies in medical and community education directed towards the welfare and social needs of the aged.

(*e*) General hospitals and, in particular, teaching hospitals must be included in the educational programme by the establishment of psychiatric early diagnostic and treatment centres.

(*f*) Teaching hospitals should make provision for satisfactory out-patient units and day hospital treatment, rehabilitation and community psychiatric services.

(*g*) A comprehensive psychiatric service should be established at selected non-teaching general hospitals according to population needs and distribution.

(*h*) Community psychiatric services, including out-patient departments, should be centralized in units close to teaching or general hospitals and, preferably, within their precincts. These facilities must be available to all members of the community.

(B) *Early Intensive Treatment.*

Facilities for early intensive in-patient treatment should be established so that patients will be encouraged to seek help.

(C) *Long-Term Treatment.*

(*a*) Appropriate hospital and sufficient community facilities, such as hostels, sheltered workshops, after-care services, etc., must be available to provide lengthy psychiatric care for the more chronic forms of mental illness.

(*b*) Rehabilitation facilities must be incorporated into community and hospital services to assist patients towards

social adaptation and restoration to a useful and satisfying place in the community. These facilities must be extended to the mentally retarded group as well as to those who are mentally ill. Rehabilitation in certain selected locations should extend to the prevocational and vocational fields.

(D) *Geriatric Patients.*

(*a*) Geriatric patients accommodated in mental hospitals should be classified with the objective of transferring suitable persons from mental hospitals to alternative accommodation external to mental hospitals.

(*b*) Where there is no alternative accommodation, special accommodation and facilities must be provided within mental hospitals.

(*c*) This accommodation should be sited with the ultimate aim of the area being degazetted.

(E) *Function of Mental Hospitals.*

The function of individual mental hospitals should be redefined in the light of the principles enumerated so that they will be put to the most useful and positive purpose.

2. Integration of Services.

(A) *State Psychiatric Services.*

The Division of State Psychiatric Services should extend its activities into the community rather than concentrate almost exclusively upon the administration of mental hospitals.

(B) *Public Health Services.*

Decentralization of public health services should envisage the provision of in-patient and out-patient treatment in the base general hospital in each health district where there is no existing mental hospital.

(C) *General Hospitals.*

(*a*) Existing facilities of general hospitals should be used to establish out-patient and in-patient services.

(*b*) In certain country locations where there are existing mental hospitals, the psychiatric services at the general hospitals should provide for out-patient departments, serviced professionally by psychiatrists from the mental hospitals, as well as by those in private practice, if they are available.

(*c*) In country areas where there are no established mental hospitals, the prototype psychiatric unit at the general hospital should consist of an in-patient section for early treatment as well as an out-patient department.

3. Immediate Projects.

(A) *City of Parramatta.*

The establishment of a comprehensive psychiatric service in the City of Parramatta.

(B) *Broughton Hall Psychiatric Clinic.*

A complete adult psychiatric service, including an out-patient department and a psychiatric community unit, should be established as an immediate priority to serve both Broughton Hall Psychiatric Clinic and Callan Park Mental Hospital.

(C) *Callan Park Mental Hospital.*

Consideration be given to Callan Park being divided into four functioning units.

(D) *Institute of Psychiatry.*

The concept of an Institute of Psychiatry by a grouping of the psychiatric units of the Broughton Hall Psychiatric Clinic and the reconstituted Callan Park Mental Hospital to provide teaching and research facilities for the University medical faculties of both Universities be encouraged.

(E) *Psychiatric Services in Teaching Hospitals.*

In each teaching hospital provision should be made for a therapeutic trinity for early intensive in-patient treatment, an out-patient department devoted exclusively to psychiatry, and one or more community psychiatric centres, including day hospital or hospitals.

(F) *Staffing.*

A further effort should be made to recruit psychiatrists throughout Australia and, if necessary, overseas, under specific guarantees of employment.

Out of the Past.

BUBONIC PLAGUE

[From the *Australasian Medical Gazette*, July 20, 1903.]

ON June 22nd a case of plague occurred at Annandale. The patient was a lad residing in Annandale and employed in an establishment in the city. The patient was removed to the Coast Hospital. He has progressed favourably. At a special meeting of the Board of Health on June 22nd it was reported that since the first infected rat was caught in Sussex-street at the commencement of the present outbreak 110 rats and mice infected with the plague had been caught. Over 50 of the rats came from stables at Waterloo. On June 24th the Premier decided to adopt the recommendation of the Board of Health that a capitation fee of 6d. be paid for rats and mice, in order to induce a vigorous crusade against the vermin, and to merely minimise the possibility of the plague spreading. This arrangement came into operation on June 29th. At the close of the day 523 rats and 309 mice were paid for. This number does not include the large number brought to the bacteriological laboratory by the staffs of men employed by the Board of Health and the City Council. Another case of plague was reported from Summer Hill early in the month. Plague-stricken rats were found a few doors from the establishment in Sussex-street where this patient worked some weeks ago, and rats were stated to be dying in some numbers at the next door premises quite recently. Eight carcases of rats and a few mice, besides some living mice were forwarded to the laboratory of the Department of Public Health for examination. A rat obtained from a Sussex-street produce store, hitherto not infected, was found to have suffered from plague. This was the only plague rat caught in the city for a fortnight. During the fortnight ended on July 8th 485 rats and 475 mice have been caught in all parts of the city by the Council's rat-catching staff and forwarded to the Department of Public Health for examination. . . . No further cases of the disease in human beings had been reported to date.

Medical Societies.

AUSTRALASIAN MEDICAL STUDENTS' ASSOCIATION.

The Melbourne Convention, 1961.

DURING the May vacation, 1961, the second annual convention of the Australasian Medical Students' Association was held at the University of Melbourne. Over 300 students from every Australian medical school, including those of Monash University and the University of New South Wales, attended.

In a brief summary on the first day, the Lord Mayor of Melbourne, Councillor Bernard Evans, welcomed the interstate visitors and officially opened the convention. Mr. Geoffrey Newman-Morris, the President of the Victorian Branch of the British Medical Association, which was the patron of the convention, then wished the Association success for the future, and Professor L. J. Ray, Professor of Anatomy in the University of Melbourne, promised the cooperation and assistance of the Faculty to the Association.

Throughout the week, lectures were held. Topics were chosen which would be of interest to the student at all levels of training, and which are not emphasized in the normal academic curricula. The lectures given were as follows; "The Biochemical Origins of Life", Mr. J. Legge; "Psychiatric Problems of Medical Students", Dr. A. J. M. Sinclair; "Experimental Surgery", Mr. George Stirling; "The Edinburgh Murders", Professor K. F. Russell; "Marriage Counselling in General Practice", Dr. W. L. Carrington; "Hydatid Disease", Professor G. S. Christie; "What is Man?", Sir John Eccles; "Auto-Immune Disease", Sir Macfarlane Burnet; Symposium, "Sex and Intersex", Dr. A. J. M. Sinclair, Dr. M. Blackwood, Dr. I. Martin.

As well as the lecture programme, special delegates from each university held a Progressive Seminar on Medical

Education, and as a result of their discussion, the A.M.S.A. has established a standing committee on medical education. This will provide proper service, both to the medical profession as a whole and to medical teaching staff, in the presentation of undergraduate thought and opinion on medical education.

An extensive social programme occupied most evenings, and included a cocktail party, a dance, a picnic in the Dandenongs, and a river trip and barbecue. A formal dinner was held at the University of Melbourne, and Mr. G. Newman-Morris and Dr. A. J. M. Sinclair were among the official guests. The guest speaker, Mr. Douglas Donald from Prince Henry's Hospital, combined the necessary entertainment with more serious reflections on the problems he considered likely to face the medical profession in the near future.

During the week the students visited many hospitals and institutions in Melbourne, including the four teaching hospitals, Royal Park and Kew Receiving Houses, the Commonwealth Serum Laboratories, the Walter and Eliza Hall Institute of Medical Research and the National Gallery. Complementary tickets for a league football match were also issued to interstate visitors.

The Convention concluded with the annual general and council meetings at which the University of New South Wales Medical Society and the Monash University Medical Undergraduates Fraternity were formally welcomed to membership of the Association, bringing the number of members to seven.

PÆDIATRIC SOCIETY OF VICTORIA.

A MEETING of the Pædiatric Society of Victoria was held at Prince Henry's Hospital, Melbourne, on September 14, 1960.

Treatable Endocrine Disorders.

DR. L. SLOAN presented two patients with treatable endocrine disorders, the diagnosis of which had been delayed.

Adreno-Genital Syndrome.

The first child was a boy, aged nine and a half years, who had been referred to Prince Henry's Hospital for investigation by a general practitioner in a country town. He had recently taken over the practice, and the boy had been brought in for treatment to a lacerated hand. He could not help but notice the boy's abnormal growth and sexual development, and after examining him, had sent him to Melbourne. The child's mother had noticed that he had been a big baby, and that his weight, height and general muscular development had always seemed in advance of his age group. At the age of five years, hair had begun to grow across his pubis and under his armpits, whilst over the preceding year he had had a persistent acneiform eruption over his face and back. His voice had always been rather deep and his penis large. It was the mother's impression that the patient's actual height had changed little over the preceding two years.

On examination, the patient showed well-developed muscular growth and skeletal growth, and, though tall, he presented a somewhat stunted appearance. Secondary sexual characteristics were pronounced, and acne was present. He had a large penis (or, perhaps better termed, phallus) with apparent hypospadias. No testes were palpable, but the skin below the penis was wrinkled and thickened. The hæmoglobin value was 16·6 grammes per 100 ml., and the white cell count was 6500 per cubic millimetre, differential count being normal. The serum electrolyte levels in mEq/l. were: sodium, 136; potassium, 4; chloride, 103; bicarbonate, 20. The blood urea level was 43 mg. per 100 ml., and the fasting blood-sugar level was 70 mg. per 100 ml. Microscopic examination of the urine revealed no abnormality. X-ray films of the skull and chest revealed no abnormality, and his bone age was estimated to be 15 years, most epiphyses being fused. Intravenous pyelography and retroperitoneal pneumography revealed no abnormality; the urinary 17-ketosteroid excretion in 24 hours was 40·2 mg.; after 10 days' treatment with 50 to 75 mg. of cortisone, this level dropped to 14·7 mg. in 24 hours; the urinary pregnantriol excretion was 35 mg. in 24 hours. The buccal-smear nuclear-sex pattern was female; the blood pressure was normal.

Dr. Sloan said that the child therefore had the clinical manifestations of virilization, accelerated growth and abnormal genitalia in a boy who was actually a female. The urinary levels of 17-ketosteroids, their fall with the administration of cortisone and the very high urinary level of pregnantriol left little doubt that he had congenital adrenal hyperplasia. Further, his apparent cessation of growth over the preceding two years, together with the radiological evidence of premature closure of the epiphyses, indicated that he had probably reached his maximum height, which was 143·5 cm. (4 ft. 8·5 in.). With regard to management, it was obvious that the child must continue to be reared as a boy. Dr. Sloan had not told the parents about the female sexing, but had simply explained to them that the patient would not be able to have any children, that he had just about reached his maximum height, and that his masculine features would always be prominent, causing him to shave early. Mr. Gunter had been asked to examine the patient's "hypospadias" — he had thought that no surgery was indicated, as the urinary stream was normal if the patient elevated his phallus. Dr. Sloan was concerned about the need for a laparotomy and the removal of the gonads, and the use, if any, of steroid therapy. He wondered if there was any possibility that the patient would menstruate, or whether the degree of androgenic activity was sufficient to prevent it. Cortisone was certainly not going to promote much bony growth, and it was doubtful, considering its dangers, whether it was justified to use it to lessen the degree of virilization. It would be wise to remove the uterus and ovaries, as there was some risk of other complications later in adult life. It would be easy enough to explain to the parents. In concluding, Dr. Sloan thanked Dr. Howard Williams and the Clinical Research Unit at the Royal Children's Hospital for performing the urinary pregnantriol estimation, and Dr. Alan Williams for his ever-reliable opinion on the buccal smears.

DR. H. BREIDAHL said that Cox and Finkelstein, of Sydney, had been the first to show that the level of pregnantriolone in the urine indicated whether hyperplasia or neoplasia of the adrenals was present. There were different types of adrenal hyperplasia, since some patients lost salt, but not others, and there were varying degrees of virilization. Dr. Sloan's patient was a male psychologically and somatically, and therefore had to continue to be reared as a male. The treatment depended on the patient's previous rearing and on his age when examined. Cortisone was indicated when the genitalia were amenable to feminization. "Medrol" given by mouth was as effective as depot implants of cortisone. He thought that laparotomy and gonadectomy were advisable because of the possibility of feminization in later life. Plastic testicles could be inserted to complete psychological masculinity.

DR. H. WETTENHALL said that there was nothing to suggest that feminization would occur, and he would not recommend laparotomy.

MR. G. GUNTER said that one objection to the implantation of plastic testicles was that "Polythene" was a possible carcinogen.

DR. M. ROBINSON said that the chromosome pattern in the condition under discussion was that of a normal female.

DR. H. WILLIAMS said that a similar patient of his had a stunted stature, but had a normal attitude to life, and had done well in under-age sprint races. The parents of such children should be told of their sterility, and they should tell the child at an appropriate age.

Craniopharyngioma.

Dr. Sloan's second patient, a boy, aged 10 years, had first been taken to the local doctor at the age of about six years because his mother had been worried about his poor appetite, and the fact that he was underweight (34 lb. or 15·4 kg.) and that he seemed very small for his age. His actual height was not known to his mother, but a photograph taken at that time with his class mates indicated his small stature. From the age of seven years, he had had vomiting attacks about every six weeks. They seemed to be precipitated by fatigue and possibly by fatty foods, and about six months later frontal headache had become a periodic feature. His appetite had improved somewhat, but his growth and weight remained more or less stationary. At the age of eight years he had weighed 38 lb. (17·2 kg.). Headaches and vomiting had become more frequent, and he would lie down and sleep at odd times. In April, 1959, when he was aged nearly eight and a half years, at the time of the eclipse he had complained of sore eyes, and his mother had noted that the right eyelid was drooping. He had again been examined by his doctor, and had later been admitted to Prince Henry's Hospital.

On examination, the patient was found to have a partial right third nerve palsy. No papillœdema was evident, and the visual fields were normal. X-ray examination of his skull had shown small areas of calcification filling the pituitary fossa. The bone was radiologically estimated as five years. Dr. Schwieger had carried out a pneumoencephalographic examination, which had shown gross displacement of the third ventricle from below by a huge filling defect in the suprasellar region. Subsequently the patient developed left-sided hemianopia, and there was some evidence of left hemiparesis.

In May, 1959, Mr. Curtis performed a ventriculocisternostomy. In early June the child became much more drowsy, and papillœdema was evident. Three weeks after the first operation a craniopharyngioma was removed through a right frontal osteoplastic flap. After operation the patient gradually improved; the left hemiparesis resolved, and the right ptosis, which had been complete, eventually disappeared. The child was given small doses of cortisone and thyroid, but much trouble was experienced with polydipsia and polyuria. He was drinking up to 15 pints of fluid each day and passing at least equal amounts of urine. It was hoped that the condition might settle after some weeks, but it had persisted. Otherwise he had made steady progress since the operation. In 15 months, his weight had risen from 15·4 to 25 kg. (55 lb.), whilst his height had increased by 8 cm. (just over 3 in.). He had injections of pitressin tannate twice a week. Dr. Sloan had tried several times to stop this therapy, but on each occasion his fluid intake had risen rapidly, causing much embarrassment at school. The patient still had small doses (which were almost homœopathic) of cortisone and thyroid, but it was intended to stop those drugs. The persistent diabetes insipidus, for which there had to be some intact anterior pituitary lobe function, further indicated that such medication was unnecessary. The child still had a partial third nerve palsy, but he was otherwise very well, with no other specific complaints.

DF. H. BREIDAHL said that the early diagnosis of that condition was always difficult. There was usually no indication to examine the skull radiologically prior to the onset of headache and vomiting. The patient's sleepiness had probably been due to hypothyroidism, which was common in adults with panhypopituitarism; his failure to grow was also evidence of hypothyroidism. By contrast, in the Lorrain-Levi type of dwarfism (by which he meant idiopathic hypopituitarism, in which there seemed to be a deficiency of growth hormone without any impairment of thyroid or adreno-cortical function), replacement therapy was not needed. With regard to the patient's diabetes insipidus, pituitary snuff could be used to tide the patient over at night or in addition to pitressin given intramuscularly. "SU4885" could be used to establish the diagnosis of panhypopituitarism beyond doubt. Cortisone and thyroid were always indicated when that condition was present.

DR. H. WETTENHALL said that Mr. R. Hooper had removed craniopharyngiomas from three patients at the Royal Children's Hospital. Each of them had had severe polydipsia and polyuria, commencing about one week after the operation. None of the patients subsequently required treatment with pitressin, as the symptoms had gradually subsided. He had found pituitary snuff a useful preparation; one patient had required intramuscular injections on alternate days, but had been subsequently well controlled on snuff four times a day. Patients with primary hypopituitarism, who were nearly always male, did not require either steroids or thyroid.

DR. R. SOUTHBY said that when there was any doubt at all that a child's growth was abnormal, an X-ray examination of the skull should always be made early.

MR. R. LOWE added that if doubt persisted, the X-ray examination of the skull should be repeated. He pointed out that craniopharyngioma was a much less common condition than cystic tumour of the pituitary fossa.

Hæmatological Conditions.

DR. R. LEWIS presented two cases of hæmatological interest.

Red Cell Aplasia.

The first patient was a male, who was aged 10 weeks when first examined in August, 1959. The pregnancy had been normal, and had gone to full term; labour had been prolonged for 34 hours, but had been otherwise normal. During her pregnancy his mother had experienced vomiting and abdominal pain, but had not been exposed to radiation or to drugs. The baby had been jaundiced for five days after birth, but the jaundice had resolved spontaneously. There was no evidence of any bleeding. He had been breast fed and had thrived well, but had always been pale. His immediate history had been of one and a half days' listlessness, pallor and fever.

On examination of the child, he was pale and listless; his temperature was 37·2° C., and his pulse rate was 160 per minute and the pulse was of poor volume. He had a mild umbilical infection. Investigations gave the following results. The hæmoglobin value was 3·4 grammes per 100 ml. The white-cell count was 6400 per cubic millimetre, and platelets numbered 680,000 per cubic millimetre. Examination of a blood film revealed anisocytosis, poikilocytosis and normochromic anæmia. Coomb's test produced a negative result. The blood group was O, Rh-positive. An X-ray examination of the chest revealed no abnormality, and an examination of the bone marrow showed an almost complete absence of red-cell precursors with only an occasional normoblast; leucocyte precursors were plentiful, and the megakaryocytes were normal.

The child was given a transfusion of 300 ml. of blood, after which his progress was satisfactory, and he was discharged from hospital with a hæmoglobin value of 15·9 grammes per 100 ml. Subsequently his hæmoglobin value fell to a level of 4·6 grammes per 100 ml. He was therefore readmitted to hospital 10 weeks after his first discharge, with a history of diarrhœa of one week's duration, which was proved to be due to a salmonella infection. On that occasion he was treated with dietary measures for the control of the diarrhœa, and was given 500 ml. of blood. As there had been reports of apparent cures of the condition of red-cell aplasia with steroids, he had been given 2·5 mg. of prednisolone twice a day ever since. His hæmoglobin value at the time of his second discharge from hospital was 15·9 grammes per 100 ml. There was then a steady fall in his hæmoglobin value for some four to five weeks; but then there was a spontaneous remission, and his hæmoglobin value rose steadily to 12·6 grammes per 100 ml. Prednisolone therapy had been continued throughout.

DR. I. EPSTEIN said that he accepted the diagnosis of red-cell aplasia in the case as being certain, there being no erythropoiesis owing to a selective deficiency of the red-cell precursors. That occurred as a developmental abnormality, and also as an acquired condition in adults, when it was related to the presence of a thymic tumour and relieved by removal of the tumour. Although some patients improved with the exhibition of steroids, it was difficult to assess whether the improvement in the present case had been due to steroids, as there had been a latent interval preceding the improvement, and as spontaneous remission was known to occur. If a further marrow examination revealed no abnormality, he would advise gradual cessation of steroid therapy. In some patients androgens had been found helpful. Dr. Epstein cited the case of a patient with red-cell aplasia who had required repeated blood transfusions for some years, but who had remained well after taking a patent vitamin preparation.

DR. L. TAFT said that the case presented emphasized how little was known of the factors governing red-cell production. The age of onset of the disease was of interest, as it indicated the possibility that a humoral agent from the mother acted as a stimulus to red-cell production. At the age of two months the red-cell count fell as a normal phenomenon. It seemed established that prednisolone did have a marrow-stimulating effect.

Thalassæmia.

Dr. Lewis then presented his second patient, a male, who had been aged 18 months when admitted to hospital in August, 1959. He had been born of an Italian mother, and adopted at the age of two weeks. Anæmia had been noted at the age of two months, and he had been receiving iron for about nine months. He had suffered two or three infections, having had measles at the age of one year and an upper respiratory tract infection at the age of 14 months. Two weeks prior to his admission to hospital he had had a fever and a cough, which had not responded to treatment.

On examination of the child, his temperature was 38·6° C. and his pulse rate 128 per minute; the respirations numbered 40 per minute. He had evidence of a mild upper respiratory tract infection, generalized lymphadenopathy and pronounced hepatosplenomegaly. The hæmoglobin value was 8·1 grammes per 100 ml., the white cell count 11,000 per cubic millimetre and the level of alkali-resistant hæmoglobin 35%. Examination of a blood film revealed hypochromia.

polychromasia, anisocytosis and poikilocytosis; some "target cells" were seen and 18 normoblasts per 100 white cells were present. No sickle cells were seen. Examination of his bone marrow revealed an increase in the number of red-cell precursors. An X-ray film of the chest showed slight enlargement of the superior mediastinum, and X-ray films of the skull and wrists revealed no abnormality.

The investigations thus indicated a leuco-erythroblastic anæmia, the increase of red-cell precursors in the bone marrow biopsy suggesting hæmolysis or severe hæmorrhagic change. The mediastinal enlargement in the X-ray film of the chest was noteworthy, as were the normal X-ray findings in the skull and wrists. The alkali-resistant hæmoglobin or fœtal hæmoglobin, which was normally absent at the age of eight months, was 35%. His mother had been traced, and her blood was found to have a level of alkali-resistant (or fœtal) hæmoglobin of 10%. The findings were considered consistent with a diagnosis of thalassæmia major in the child and of thalassæmia minor in his mother.

With rest in bed the patient's fever resolved, and the hæmoglobin value improved spontaneously from 8·1 to 10·8 grammes per 100 ml. He was readmitted to hospital three months later, with a history of irritability and an enlarging abdomen. On examination of the child, his temperature was 31·8° C. and the spleen had enlarged further, being in the left iliac fossa; the liver was palpable three fingers' breadth below the costal margin. On that occasion the hæmoglobin value was 7·7 grammes per 100 ml. He was given a transfusion of 150 ml. of blood, and because of the mechanical effect of the splenomegaly, splenectomy was performed. Histological examination of the spleen showed cords of hæmatopoietic tissue and nodules from the hilum, which were proved to be lymph nodes containing hæmatopoietic tissue. The spleen was grossly enlarged, measuring 19 by 12 by 7 cm., and weighed 625 grammes after fixation.

The child was admitted to hospital for the third time five months later, when he had had two weeks of irritability, anorexia and listlessness. The temperature on that occasion was 37·5° C., no glands were palpable, and the liver was palpable two fingers' breadth below the right costal margin. The hæmoglobin value was 7·6 grammes per 100 ml., and the blood film indicated a further hæmolytic crisis, there being very numerous nucleated cells in the peripheral film, most of which were normoblasts. The reticular cell count was 30%. An X-ray examination of his chest showed generalized cardiac enlargement and gross widening of the superior mediastinum, which was presumed to be due to mediastinal glandular enlargement. He was given a transfusion of 350 ml. of blood, and the hæmoglobin value had risen to 11·6 grammes per 100 ml. on his discharge from hospital. Since then it had steadily fallen to a level of 8·3 grammes per 100 ml.

Dr. Lewis said that the prognosis was, of course, poor. Debatable points were whether the splenectomy should have been performed, in view of the fact that the child had been practically an appendage to his spleen, and secondly, what was the mechanism of the congestive cardiac failure.

DR. I. EPSTEIN said that the problem of the congenital hæmoglobinopathies was becoming more frequent. The features of thalassæmia major were so classical that diagnosis was relatively easy. However, thalassæmia minor, in which the patient was heterozygous for the abnormal gene, was often difficult to diagnose, the patient frequently first presenting himself in adult life. The race of the patient and the presence of splenomegaly were helpful pointers to the diagnosis. Estimation of the serum iron concentration was useful in differentiating the condition from iron-deficiency anæmia, patients with thalassæmia having a high serum level of iron. Dr. Epstein agreed that splenectomy had been wise in Dr. Lewis's case, as it had at least given the child several months of comfort. At the same time, it had removed a large part of the patient's "red-cell factory", and had thus led to the further development of extramedullary hæmatopoiesis at other sites.

DR. L. TAFT said that the patient had been unusual in having normal skull X-ray findings; of 30 cases, he had seen not one in which that had occurred. Thalassæmia was an odd disease in having a very wide spectrum of severity. It was probable that a number of genetic abnormalities were concerned. Electrophoresis and the finger-print technique of hæmoglobin analysis were helpful investigations. He pointed out that fœtal hæmoglobin could be found in conditions other than thalassæmia—for instance, leukæmia. He had seen spectacular general progress occur after splenectomy. The child's cardiac failure was probably due to cardiac hæmosiderosis.

Correspondence.

THE MERVYN ARCHDALL MEDICAL MONOGRAPH FUND.

SIR: I hope your editorial plea will achieve generous support for the Mervyn Archdall Medical Monograph Fund, not only in recognition of the Fund's valuable rôle, but as a richly-deserved and appropriate tribute to a man to whom we are all in some measure indebted, directly or indirectly.

As the author of one of the monographs to which you generously refer, I might perhaps be allowed to express my personal appreciation of the advice and encouragement given me over the years by Dr. Archdall. In addition to his practical help, of which the publication of the monograph is only one example, I became most grateful to him for stimulating my interest in medical editing and medical writing. In these fields, as in that of Australian medical history, the study of which he advocated so warmly in the editorial columns, there are certainly others better qualified than I who would acknowledge the value of his enthusiastic leadership. I merely wish to record the lasting impression made by his generous assistance of a very junior graduate at first unknown to him personally.

Yours, etc.,

386 Albert Street,
East Melbourne.
July 26, 1961.

BRYAN GANDEVIA.

THE MANAGEMENT OF RUPTURED ABDOMINAL ANEURYSMS.

SIR: Regarding the article entitled "The Management of Ruptured Abdominal Aneurysms" by Professor R. P. Jepson and Mr. R. A. Rieger. Rupture of an abdominal aneurysm is a surgical emergency, the clinical features of which are not as widely recognized as they might be, and I would compliment the authors of this article on bringing this subject to notice. They make an important point that most of these aneurysms leak before frank rupture occurs, and that, whilst surgical excision undertaken in the face of profound shock is an almost hopeless procedure, resection of the aneurysm in the leaking phase results in the survival of most patients.

If I may make so bold, I would like to add one point to the discussion of the clinical picture, and that is to say that the leaking aneurysm not infrequently mimics renal colic, and in an obese patient, where the aneurysm may be difficult to palpate, the diagnosis may be overlooked. In a small personal series of 12 aneurysms this feature has been present in two cases, and in both the diagnosis was delayed whilst investigation of the renal tract was carried out. It would seem that, whenever an apparent renal colic is accompanied by features of shock, the alternative diagnosis of leaking abdominal aneurysm should be critically considered.

Yours, etc.,

14 Parliament Place,
Melbourne, C.1.
July 27, 1961.

NEIL JOHNSON.

PENICILLINASE AS A PHARMACEUTICAL BENEFIT.

SIR: Mr. Preiss of Riker Laboratories has drawn attention to the low incidence of serious side effects to "Neutrapen" brand of penicillinase (MED. J. AUST., 1961, 2: 73). There are several points in his letter, however, to which I must refer. I did not state that several reports of reactions to penicillinase had appeared. Few reports certainly have appeared in the literature, but unfortunately all interesting clinical material is not published. During a recent trip abroad I found that some physicians were most reluctant to use penicillinase at all on account of some toxic and some quite severe allergic reactions (not to be confused with "idiosyncracy").

Penicillinase is a potent antigen, and the likelihood of its producing sensitivity and subsequent reactions should be considered whenever it is prescribed, and all steps taken to reduce this likelihood when it is being administered.

Mr. Preiss states that the antibodies produced by "Neutrapen" would probably by clinically insignificant. I can see no reason to assume that they would be, however much "Neutrapen" is purified. With regard to subsequent courses of penicillinase, probable allergic reactions do not depend on the amount of protein remaining as Mr. Preiss suggests, but on a state of tissue sensitization.

I also mentioned that when "Celbenin" ("BRL 1241") was used, greater care than ever should be exercised in excluding possible penicillin allergy in any patient, as penicillinase may be incapable of dealing with subsequent allergic reactions. The article in *The Lancet* referred to by Mr. Preiss describes penicillinase as inactivating "Celbenin" at a very much slower rate than penicillin G. If this occurs *in vivo*, as is likely, then the care that I have urged before prescribing "Celbenin" is surely still warranted.

Penicillinase is a most valuable, and perhaps on occasions a life-saving drug, but it would be unwise to ignore its potential hazards or limitations.

Yours, etc.,

R. MUNRO FORD,
Honorary Allergist, Royal Adelaide Hospital.

163 North Terrace,
Adelaide.
July 26, 1961.

PHYSIOTHERAPY IN THE CARE OF BED-RIDDEN PATIENTS.

SIR: There are many bed-ridden chronically sick, most in the evening of their lives, who are looked after by their families and/or home-nursing services, or are in convalescent homes or cottages for the aged. It is likely that many of these do not need to stay bed patients were an adequate physiotherapy service provided. To make these old people walk, if only a few steps, lessens mental regression, provides increasing happiness to them, and helps the physical difficulties of decubitus ulcers and daytime incontinence.

The hemiplegic of today is hardly rehabilitated with the shortage of hospital beds and the consequent fast discharge taking place. He may be asked to travel or be conveyed long distances to a public hospital for this. These institutions may provide good care of acute illness, but after-care is too often impersonal, with the attitude that the patient over 55 makes unrewarding progress. The resultant fall of patient morale leaves the family doctor fighting relatives to make the patient ambulatory, hindered by lack of a physiotherapy service because of distance, but helped by home-nursing services.

There are many difficulties in the provision of a domiciliary physiotherapy service. The cost of private physiotherapy in the home does not commend itself to the public if it does not attract an insurance benefit similar to that enjoyed by the medical services. Rehabilitation of the aged is time-consuming and unremunerative by comparison with workers' compensation cases.

The most useful immediate solution would seem to be the provision of a physiotherapy service in conjunction with existing home-nursing services. This would require Government support. The initial insufficiency of physiotherapists at present for this task is appreciated—but there are many now married not practising who may be induced to undertake such work part-time.

Yours, etc.,

JAMES WATSON.

Cnr Ley and Wooltana Streets,
South Como,
Western Australia.
July 23, 1961.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Refresher Course in Obstetrics and Gynæcology.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that a refresher course in obstetrics and gynæcology will be held at the Women's Hospital, Crown Street, Sydney, from Monday to Friday, August 28 to September 1, 1961, under the supervision of Dr. J. Newlinds. Enrolments are limited to 10 post-graduate students in residence and 14 attending as external students. Fees are £8 18s. 6d. (including board and residence) or £6 6s. (external attendance). Candidates may take up residence on Saturday afternoon, August 26. Early application, enclosing remittance, should be made to the Course Secretary, the Post-Graduate Committee in Medicine, Herford House, 188 Oxford Street, Paddington. Telephone: 31-0671. Telegraphic address: "Postgrad Sydney". The detailed programme is as follows:

Monday, August 28: 9 a.m., welcome by chairman of staff, Dr. F. A. Bellingham; 9.30 a.m., "Non-Physiological Amenorrhœa", Dr. R. Mackey; 11.15 a.m., demonstration of cases in the labour ward; Dr. P. Crowe; 2 p.m., "Abortion", Dr. D. H. McGrath; 3.15 p.m., "Complications in Obstetrics and Gynæcology", Dr. W. McBride.

Tuesday, August 29: 9.30 a.m., "Vaginal Discharge", Dr. S. Devenish Meares; 11.15 a.m., gynæcological ward rounds, Dr. F. A. Bellingham; 2 p.m., demonstration in the Sterility Clinic, Dr. Alan Grant and Dr. R. Mackey.

Wednesday, August 30: 9.30 a.m., "Coping with the Rh-Negative Mother", Dr. F. A. Bellingham; 11.15 a.m., cases and demonstration in the Cancer Clinic; 2 p.m., "Hæmorrhage During Pregnancy", Dr. R. Bowman; 3.15 p.m., Pædiatric Department—Dr. S. E. L. Stening, Dr. C. W. G. Lee and Dr. R. H. Vines.

Thursday, August 31: 10 a.m., Medical Clinic, Dr. Helen Taylor and Dr. T. I. Robertson; 11.15 a.m., "Preeclamptic Toxæmia", Dr. M. T. Drummond; 2 p.m., "Breech Delivery", Dr. R. Macbeth; 3.15 p.m., demonstration of vaginal cytology in the Pathology Department, Dr. J. Murray Moyes.

Friday, September 1: 9.30 a.m., obstetric ward rounds in the ante-natal wards: Dr. Alan Grant; 11.15 a.m., round-table conference on progestogens—"Bring your Problems", Dr. Alan Grant and Dr. J. Murray Moyes; 2 p.m., demonstration of cases in the labour ward, Dr. S. B. Robertson.

All Cæsarean sections will be demonstrated as they occur. All operations will be on closed-circuit television.

Annual Subscription Course.

The following lectures are open to members of the annual subscription course: Thursday, August 10, 8 p.m., Dr Andre B. Ballard, Associate in Psychiatry, College of Physicians and Surgeons, Columbia University, New York—"Family Diagnosis and Family Therapy", I.C.I. Theatrette, East Circular Quay. (Arranged in conjunction with the New South Wales Association for Mental Health and the Psychiatric Rehabilitation Association.) Monday, August 14, 11.30 a.m., Professor J. E. Caughey, Associate Professor in Neurology, University of Otago, New Zealand, and Guest Lecturer to the Royal North Shore Hospital of Sydney Reunion Week—"The Management of Acute Cerebrovascular Accidents", Students' Common Room, The Royal North Shore Hospital. Wednesday, August 16, 2.15 p.m., Professor J. E. Caughey—"Muscular Dystrophies", Students' Common Room, the Royal North Shore Hospital. Friday, August 18, 2.15 p.m., Professor J. E. Caughey—"Hypopituitarism", Students' Common Room, The Royal North Shore Hospital. Wednesday, August 23, 9 a.m., Professor J. E. Caughey—case presentations and discussion, Students' Lecture Theatre, St. Vincent's Hospital; 12 noon, case presentations and discussion, Sydney Hospital; 2 p.m., "The Myopathies", Maitland Lecture Hall, Sydney Hospital. Thursday, August 24, 8 p.m., Professor J. E. Caughey—"Dystrophia Myotonica", Northcott Neurological Centre, Cammeray. Friday, August 25, 1.15 p.m., Professor J. E. Caughey—"Hypopituitarism", Scot Skirving Lecture Theatre, Royal Prince Alfred Hospital. Tuesday, August 29, 1.15 p.m., Professor Sir Derrick Dunlop, Professor of Therapeutic and Clinical Medicine, University of Edinburgh, and Norman Paul Visiting Professor for 1961 to Sydney Hospital—"The Diagnosis and Treatment of Thyroid Disease", Students' Lecture Hall, St. Vincent's Hospital. Wednesday, August 30, 8.15 p.m., Professor Sir Derrick Dunlop—"Oral Hypoglycæmic Agents", I.C.I. Theatrette, East Circular Quay. Friday, September 1, 1.15 p.m., Professor Sir Derrick Dunlop—"The Complications of Diabetes", seminar, Scot Skirving Lecture Theatre, Royal Prince Alfred Hospital. Tuesday, September 5, 2 p.m., Professor Sir Derrick Dunlop—"The Endocrine Glands and the Skin", Students' Common Room, The Royal North Shore Hospital; 8.15 p.m., Professor Robert McWhirter, Professor of Medical Radiology, University of Edinburgh, and Radiotherapist, Royal Infirmary, Edinburgh—"Cancer of the Breast", I.C.I.

Theatrette, East Circular Quay. (Arranged in association with the College of Radiologists of Australasia.) Thursday, September 7, 8.15 p.m., Professor Sir Derrick Dunlop—"The Opium Analgesics and their Modern Synthetic Alkaloids", I.C.I. Theatrette, East Circular Quay. (Arranged in association with the Australian College of General Practitioners, New South Wales Faculty.) Thursday, September 14, 8.15 p.m., Dr. Paul Wood, O.B.E., Director (part-time), Institute of Cardiology; physician, National Heart Hospital; physician, Cardiac Department, Brompton Hospital, England—"Auscultation of the Heart", Stawell Hall, 145 Macquarie Street.

The annual subscription course covers attendance at lectures by overseas lecturers and other specially arranged activities. The annual fee is £3 3s. from July 1. The fee for first-year and second-year resident medical officers is £1 12s. 6d. Last-minute alterations to meetings are notified by advertisement in *The Sydney Morning Herald* ("Public Notices"), if possible on the day before the meeting.

Method of Enrolment and General Information.

Applications for enrolment on metropolitan and week-end courses should be made to the Course Secretary, Herford House, 188 Oxford Street, Paddington.

Taxation Deductions.

Fees paid by medical practitioners, who are in practice, for attendance at revision and week-end courses conducted by the Committee, including living and travelling expenses, are deductible (Taxation File No. AF/1865).

Notes and News.

Reader's Digest International Rehabilitation Awards.

The Reader's Digest Foundation, in cooperation with the International Society for the Welfare of Cripples, has established a group of International Rehabilitation Awards, to help promote better rehabilitation of the crippled throughout the world. The awards will be presented to the nation or community that makes the most substantial progress in creating and expanding rehabilitation programmes during the two-year period 1961-1962. The awards will be open to all societies, associations or other groups concerned wholly or in part with the welfare of the disabled, in any country of the world. The winners will be those societies which have conceived and developed the best rehabilitation schemes within their own community, during the period between the announcement of the awards in August, 1960, and December 31, 1962. These schemes may be in any field affecting the welfare of the disabled. Each one will be considered by the international panel of judges in relation to the medical services in general, and to the rehabilitation facilities in particular, of the community promoting the scheme. Particular consideration will be given to: (i) the status of services in the community in 1960; (ii) voluntary leadership provided by the nation or community recognizing the needs of the handicapped and taking action to provide services; (iii) means employed to provide the needed services; (iv) action taken to remove existing prejudices hindering the development of medical, social, educational and vocational services for the handicapped; (v) development of employ-the-handicapped programmes, educational services established for crippled children and medical programmes. Seven awards will be presented at the Ninth World Congress of the International Society in Copenhagen in 1963. There will be two general awards of $2500 and $1500 each, as well as five regional awards of $500 each. Further information may be obtained from the world headquarters of the International Society for the Welfare of Cripples, 701 First Avenue, New York 17, N.Y.

Future of Commonwealth Serum Laboratories.

The Minister of Health, Dr. Cameron, has made a statement relating to the Commonwealth Serum Laboratories. He said that it was hoped to announce shortly the membership of the Commission which would administer the Laboratories. The Government had before it for consideration the names of a group of professional and business men whose services it was hoped to enlist as Commissioners. The Act which provided for the setting-up of the Commission had received the Royal Assent. It would operate from a

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED JULY 15, 1961.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	..	..	1(1)	..	..	1(1)	..	..	2
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	1	..	2	..	..	..	4	..	7
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	2	1(1)	..	..	..	..	..	3
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	1	6(5)	3(3)	..	..	..	2	..	12
Diphtheria	..	..	..	..	..	..	..	..	..
Dysentery (Bacillary)	..	2(2)	..	..	..	..	2	..	4
Encephalitis	..	..	..	1(1)	..	..	..	..	1
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	108(36)	94(22)	27(7)	8(2)	4(2)	2	..	1	244
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	1	..	5	..	..	..	..	..	6
Malaria	..	..	..	..	..	..	..	..	..
Meningococcal Infection	2	1	..	..	..	..	..	..	3
Ophthalmia	..	..	..	..	..	..	1	1	2
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	2(1)	3(2)	2(1)	2(1)	..	..	..	..	9
Puerperal Fever	..	..	..	..	..	..	..	..	..
Rubella	..	9(3)	..	1	4(4)	..	..	1	15
Salmonella Infection	..	..	..	..	2(2)	..	..	..	2
Scarlet Fever	11(8)	11(9)	3(1)	3(1)	..	..	..	..	28
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	..	..	..	..	..	..	..
Trachoma	..	..	..	..	1	..	1	..	2
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	41(22)	21(19)	6(3)	8(7)	3(2)	4(2)	..	..	83
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

date to be proclaimed, which would coincide with the appointment of the Commission. From that date the Laboratories would be controlled by the new Commission, instead of by the Commonwealth Department of Health.

Dr. Cameron said he was completely confident that the Laboratories would operate even more efficiently, in both their production and their research activities, under the new administration. The functions of the Commission would be to produce and sell a wide range of biological products, and it was authorized by the Act to undertake research towards improving the production of all its products. That authority would rest entirely with the Commission, which would be free to determine its own products-research programme, to be financed from its own resources. In addition, the Commission would undertake research outside the scope of its own products and provide potential production capacity for emergency requirements, according to Ministerial direction. The Act provided that losses resulting from compliance with such directions would be reimbursed by the Commonwealth. Of course, the Minister would be guided in issuing such directions by the advice of the Commission, and the Commission would be free to propose research projects to the Minister. The Act authorized the Commission to appoint its own staff up to salaries of £2500 a year.

Dr. Cameron said the Government expected to be able to appoint men of outstanding ability to the Commission. He used the following words:

> I have not the slighest doubt that men of this calibre, regardless of whether their experience is primarily business or scientific, will ensure that the Commonwealth Serum Laboratories are administered in the most efficient and progressive way possible. It was, in fact, to ensure the increased overall efficiency of the Laboratories, both as a production unit and a research undertaking, that the Commission proposal was advanced and given effect.

Corrigendum.

INCOMPLETE TRISOMY IN A MONGOLOID CHILD EXHIBITING MINIMAL STIGMATA.

IN the paper entitled "Incomplete Trisomy in a Mongoloid Child Exhibiting Minimal Stigmata" by P. L. T. Ilbery, C. W. G. Lee and S. M. Winn, published on page 182 of our issue of July 29, 1961, there is an unfortunate mix-up in the illustrations. Figures III and IV are, of course, the same picture with different enlargements; Figure III should have been omitted, the legend under Figure III refers to Figure IV, and that under Figure IV refers to Figure V. We apologize for the confusion.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Appel, Denis Anthony, M.B., B.S., 1959 (Univ. Sydney), Women's Hospital, Crown Street, Sydney.

Havyatt, Betty Carlisle, M.B., B.S., 1946 (Univ. Sydney), 20 Killara Avenue, Killara, New South Wales.

Whitton, James, M.B., B.S., 1960 (Univ. Sydney), Ryde District Soldier's Memorial Hospital, Denistone Road, Eastwood.

Deaths.

THE following deaths have been announced:

FAUNCE.—Edmund Alured de Laune Faunce, on July 30, 1961, at Sydney, N.S.W.

TERRILL.—Frederick Edward Terrill, at Kensington Park, South Australia.

WILSON.—Henry Maxwell Wilson, on August 2, 1961, at Melbourne, Victoria.

Diary for the Month.

AUGUST 14.—Victorian Branch, B.M.A.: Finance Sub-Committee.
AUGUST 15.—New South Wales Branch, B.M.A.: Medical Politics Committee.
AUGUST 16.—Western Australian Branch, B.M.A.: General Meeting.
AUGUST 17.—Victorian Branch, B.M.A.: Executive Meeting of Branch Council.
AUGUST 18.—New South Wales Branch, B.M.A.: Ethics Committee.
AUGUST 19.—Victorian Branch, B.M.A.: Country Branch Meeting (Geelong).
AUGUST 22.—New South Wales Branch, B.M.A.: Hospitals Committee.
AUGUST 23.—Victorian Branch, B.M.A.: Branch Council.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): Medical Officers to Sydney City Council. All contract practice appointments in New South Wales. Members are requested to consult the Medical Secretary before undertaking practice in dwellings owned by the Housing Commission.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

Authors of papers are asked to state for inclusion in the title their principal qualifications as well as their relevant appointment and/or the unit, hospital or department from which the paper comes.

References to articles and books should be carefully checked. In a reference to an article in a journal the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of article. In a reference to a book the following information should be given: surname of author, initials of author, year of publication, full title of book, publisher, place of publication, page number (where relevant). The abbreviations used for the titles of journals are those of the list known as "World Medical Periodicals" (published by the World Medical Association). If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full data in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary is stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: 68-2651-2-3.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this Journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

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